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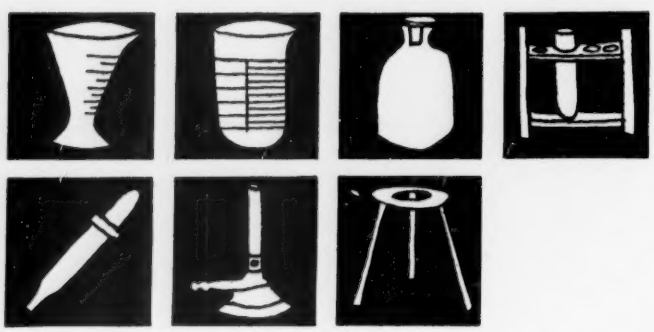

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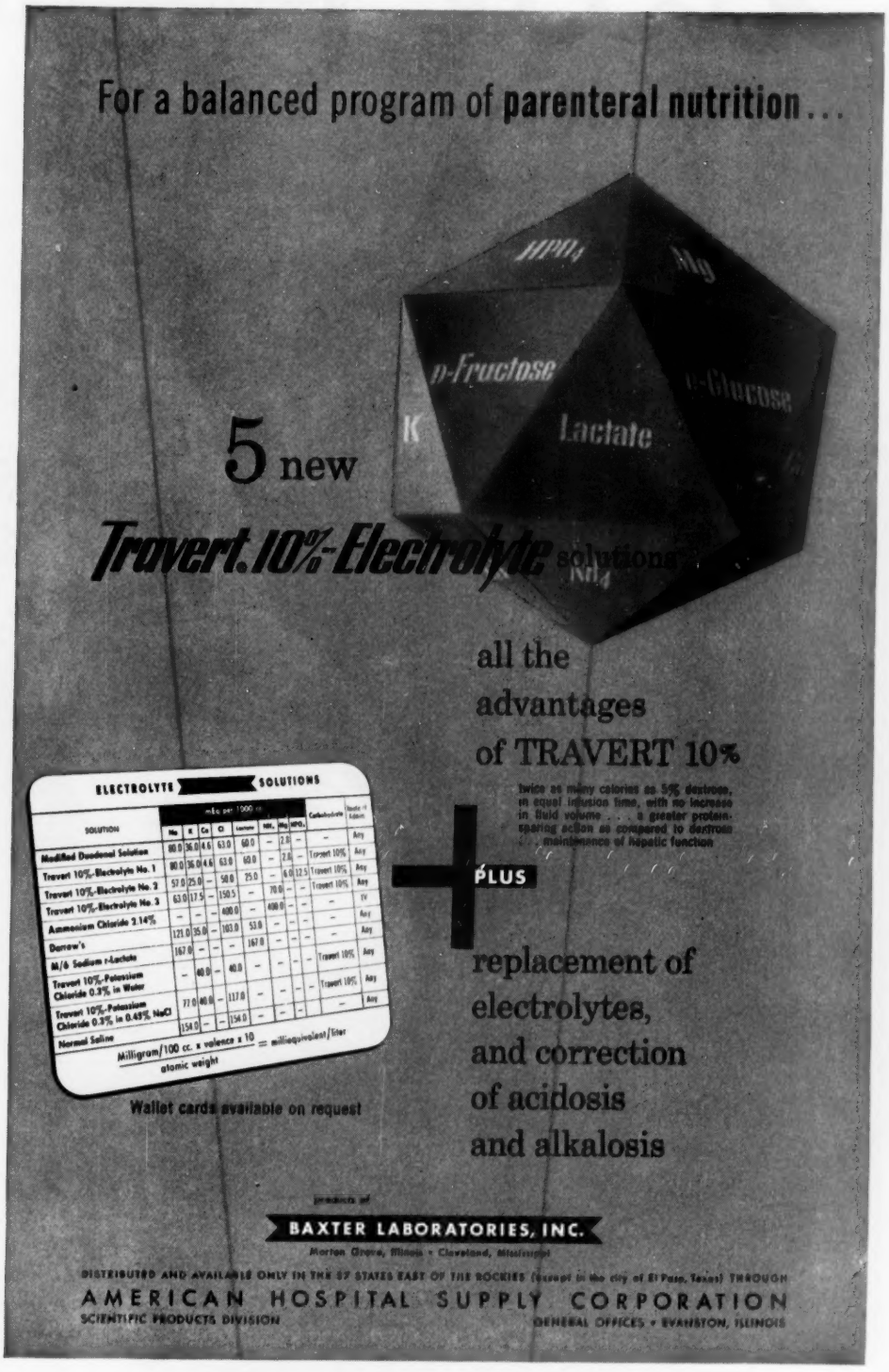
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SOME PHYSIOLOGIC ASPECTS OF DERMATOLOGIC PROBLEMS*

WALTER C. LOBITZ, JR., M.D.†

HANOVER, NEW HAMPSHIRE

THERE is an old saying that the study of clinical dermatology is the study of gross and microscopical pathology of the skin in the living. In recent years the physiology of the skin of the human being has become better understood. As a result the practice of modern clinical dermatology has become even more exciting because it encompasses not only the understanding and correlation of gross and microscopical structural changes of the skin but also the "applied physiology" of the skin.[1]

When the program chairman suggested that this discussion might include some physiologic approaches to the understanding of skin disorders, it seemed timely to stress how clinicians are utilizing this "applied physiology" of the skin in the daily study and treatment of the dermatologic patient.

So much fascinating basic physiologic material has come to light in recent years that it would be impossible to include it all in such a meeting as this.[2] Because of the limitation of time it was decided to confine the discussion to *some* of the physiologic approaches in the daily practices of medicine and dermatology. For the sake of convenience the material is presented under the headings of various component parts of the skin.

Rothman[3] has emphasized the fact that vasomotion, pilomotion and sweating are the clinical evidences that autonomic-nervous-system impulses have reached the skin. One cannot think of vasoconstriction or vasodilatation, of erector-pili responses (goose flesh) or of sweating without thinking of the emotions that are associated with these responses. Rothman has pointed out:

> The type of emotions will by no means specify the impulse. Emotions so widely different as are rage and fear, are equally liable to cause pilomotion. Blushing, though paradigmatically an expression of bashfulness or shame, is observed in anger as well. Some persons turn pale when they get mad and others redden. There are persons who at one occasion react with a red face and at another with paling for the very same emotion. A person who blushes easily responds also with increased local vasodilatation to heat stimuli but bashfulness is not necessarily the main feature of his personality.

The question then arises, Do these autonomic responses of the skin play a role either in the production of disease or in the aggravation of it?

VASCULAR RESPONSES

Certainly, the constantly changing cutaneous vascular physiology is evident when one observes both normal and abnormal skin. Physicians are constantly recognizing such vascular changes of the skin as redness or blanching and coldness or warmth in their evaluations of the clinical problems of the patient. Such correlations of color and temperature are significant when it is recalled that skin color depends on the amount and type of blood in the capillary bed whereas skin temperature is controlled by the rate of blood flow through the arteriolar bed. A skin can therefore be warm but not necessarily red, and, contrariwise, it can be red and not necessarily warm.[4]

To interpret these various clinical observations properly perhaps some of the normal cutaneous vascular responses should be emphasized.

Everyone is familiar with the triple response of Lewis and Grant.[5] When one strokes the skin firmly with a pointed, dull instrument, a red line appears within three to fifteen seconds. This phenomenon is limited to the line of stroke and is due to the direct action of the stroke on the superficial blood vessels of the skin. The second response, the flare or spreading flush, occurs a few seconds after the development of the red line, and since it is mediated by an axon reflex, an intact and functioning cutaneous nerve supply must be present. The third response is the wheal or local edema, which is preceded by and then completely replaces the red line, about one to three minutes after the initial stroke. There is evidence that such a triple response of, first, red line, secondly, flare and, thirdly, whealing is mediated by histamine or a histamine-like substance. Certainly, if histamine is introduced intradermally into the skin, the triple response is repro-

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 20, 1954.

From the Department of Dermatology, Hitchcock Clinic, and Dartmouth Medical School.

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duced. From the clinical standpoint one is then confronted with an urticarial lesion.

If acetylcholine[6] is introduced into the skin intradermally it also causes, first, a local red reaction that is due to the direct vasodilatation effect of the drug, secondly, an axon-reflex flare around this red reaction and, thirdly, in some persons, whealing. Acetylcholine, however, also produces sweating both by the direct action of the drug and by axon reflex in the same areas.

Of what significance is such basic vascular physiology? Is one clinically confronted with such redness and whealing of acetylcholine origin as well as of histamine origin? If so, how can one differentiate them, and how can they be treated?

Urticaria produced by histamine release — the so-called histaminic urticaria, for example — is seen in true allergy, in serum-sickness reactions to drugs like penicillin, as a secondary effect of systemic disease such as the malignant lymphomas and on a functional basis. These lesions can be recognized by the fact that the whealing component is quite large in relation to the small axon-reflex flare or redness around the wheal. Sometimes, the itching that is present is not too severe.

On the other hand, urticaria developed via the acetylcholine mechanism (the so-called cholinergic urticaria) has minute papular wheals, sometimes not more than 1 or 2 mm. in diameter. The ratio of wheal to flare is just the reverse of that seen in histaminic urticaria. The cholinergic urticaria flare is striking, producing a large area of redness around the minute hive in the center. The itching associated with such cholinergic urticaria is quite severe. It is interesting that to date only two major etiologic mechanisms are recognized as responsible for cholinergic urticaria.[7] They are seen in true physical allergy produced by heat and, commonly, as emotional urticaria.

From the therapeutic standpoint it is essential to differentiate these two mechanisms. An antihistamine is not the drug of choice in the treatment of cholinergic urticaria. And, by the same token, cholinergic blocking agents, such as atropine-like drugs, are of no value in the treatment of histaminic urticaria.

If the skin of a patient with atopic dermatitis is stroked firmly with a pointed, blunt instrument in the manner used to elicit the triple response of Lewis and Grant, a paradoxic reaction takes place, particularly if the disease is active. The red line appears briefly as in the normal response, but then it is immediately replaced by vasoconstriction of the same blood vessels, producing the well known white-line, or blanch, phenomenon.[6] This reaction is an important prognostic, as well as diagnostic, sign in the atopic patient. It is the first thing to appear on apparently normal skin when an exacerbation of the disease is beginning and the last sign to change to a normal triple response as the skin is healing.

It has also been shown that when acetylcholine is introduced into the skin of a patient with atopic dermatitis, vasoconstriction occurs instead of the usual vasodilatation. Whealing appears in the injected site in 100 per cent of such cases. The primary lesions that cause the intense pruritus in the atopic person are often cholinergic urticaria, but sometimes secondary lichenification and thickening of the scratched skin make it difficult to see such small urticaria. Again, anticholinergic drugs can be helpful in the management of these cases.

Sweat Glands

Just as the blood vessels of the skin normally react to cholinergic stimuli (vasodilatation) and adrenergic stimuli (vasoconstriction) sweat glands respond to these physiologic and pharmacologic stimuli.

The eccrine sweat glands,[8] which produce the true sweat, are located on all the body surfaces. Such eccrine glands, exclusive of the palms and soles, secrete in an attempt to regulate body temperature. The eccrine sweat glands of the palms and soles, axillas, groin, anogenital areas and central part of the face respond to mental work, pleasant and unpleasant. However, emotional sweating can occur on any area of the body in some persons. Secretion of these eccrine sweat glands is stimulated by acetylcholine or by other cholinergic stimuli.

The apocrine sweat glands[9] are structurally related to the lactiferous glands and embryologically are developed along with the hair follicle and sebaceous gland. These structures, which appear at puberty, are normally located in the axilla, groin, anogenital areas, around the areola of the breast and occasionally over the malar areas of the cheek, on the nose and on the anterior surface of the neck. They are the scent-producing glands of the body. The apocrine glands, for the most part, share a common opening of the skin with the hair follicles and the sebaceous glands. Unlike the eccrine sweat gland, they are stimulated by adrenergic or epinephrine-like responses of the body; the apocrine type of secretion is also quite different from eccrine sweat in that only a small, milky-white, plastic material is dumped onto the surface of the skin and then dries as a tenacious cap, 2 to 4 mm. in diameter, about the hair shaft. This is in marked contrast to the profuse, watery sweat from the eccrine gland.

The patient with axilliary hyperhidrosis, of course, does not differentiate eccrine and apocrine sweat secretions. In such cases it is of value to explain some basic facts. For example, eccrine sweat is profuse, but has no odor. Apocrine sweat has odor, particularly when it is contaminated with bacteria,[10] but the patient cannot see the small amount of milky, waxy secretion that is deposited on the skin about the hair. The emotions that cause profuse eccrine sweating do not produce axilliary odor; those that result in axillary odor do not initiate profuse sweat-

ing. Drugs that inhibit one type of axillary sweating do not inhibit the other.

It has been established in recent years, both clinically and experimentally, that the miliaria (prickly-heat) diseases (miliaria crystallina, miliaria rubra, miliaria profunda and pustular miliaria) result from the retention of sweat in the skin.[11] Any damage to the skin, mild or severe, will produce thickening in the stratum corneum that, in turn, may plug the openings of the sweat pores. Sweat is then secreted into rather than onto the skin. This clinical syndrome of sweat retention complicates and is secondary to almost all inflammatory changes in the skin. The symptom of miliaria rubra is that of a pricking, burning sensation, which immediately changes to an intolerable itch. The effect of thermal sweating on cutaneous disease is obvious. However, many of the correlations that clinicians make between the emotional reactions of the patient and the symptoms of the skin can also be explained on such a basis. The emotional component of pruritus ani and vulvae and of so-called localized neurodermatitis of the palms and elsewhere can be so explained. It is difficult enough to control environmental temperature in thermal sweating; it is even more difficult to control emotional sweating. Both types of eccrine sweating are, of course, cholinergic in origin and stimulated by acetylcholine and the so-called cholinergic emotions such as anxiety, embarrassment and resentment. Anticholinergic drugs like atropine tend to inhibit such sweating. However, Shelley and Horvath[12] have pointed out that, although atropine will decrease the sweating, it is futile to attempt to produce complete inhibition in this manner; the anhidrotic effect can be achieved only through the use of large toxic doses of atropine and even then only for a short time. On the other hand, on small sections of involved skin, as in areas of localized neurodermatitis, sweating can be arrested for several days by the intradermal injection of from 0.10 to 1 cc. of atropine (1:100,000 dilution) without the danger of any systemic action of the drug. This method then gives the clinician a means of diagnosis when it is necessary to produce an area of anhidrosis to understand the complexity of any given dermatosis.

The apocrine gland can also become obstructed, causing a clinical syndrome. The intense itching of the axilla, known as Fox–Fordyce disease, that has been so troublesome in the past is now understood to be a miliaria apocrina. Here, again, since apocrine glands are adrenergically stimulated, the use of cholinergic blocking agents such as the atropine series will be of no value in the treatment and control of the apocrine sweat retention. Theoretically, an effective adrenergic blocking agent like ergotamine or Dibenamine should be effective in this regard.

Hair

There are three main stages in the development of the hair follicle: anagen, the phase of active growth and development; catagen, the phase of growth cessation, club-hair formation and the setting aside of the dormant hair germ for the next hair generation; and telagen, the resting phase.

Hair follicles in human beings, unlike those in some animals, are not all in the same phase of development at the same time. This has retarded the understanding of hair growth and hair loss as well as explaining why the clinician has had difficulty in understanding the alopecias and diseases of the hair-bearing areas. Recently, the correlation of knowledge of hair growth, hair physiology and histochemistry of the skin[13] made it possible to demonstrate in the human being the well understood mechanisms of hair growth known to occur in the animal. For example it is now known that the type and extent of damage that can occur to hair follicles will depend entirely on their particular stage of development at the time of damage.[14] Irradiation in the anagen phase results in cessation of development of the follicle and loss of any growing hair. No such hair loss occurs in the catagen or telagen phase. In contrast repeated applications of irritants (potassium phosphate, ether, benzene and so forth) have no effect on hair in the anagen, but do cause loss of hair in the telagen phase. Pigment loss for ensuing hair generations is greatest in follicles irradiated in catagen or telagen stage. Kligman,[15] producing experimental tinea capitis of the epidemic type in children, indicates that they can infect a hair with *Microsporum audouini* only when the hair follicle is actively growing. It is also interesting that in areas of alopecia areata all the hairs have slipped into the telagen phase at one time. It is only in this telagen phase that the hairs fall out normally.

Since the studies by Myers and Hamilton[16] on the regeneration rate and growth rate of human hair the clinician has been able to give patients with certain types of alopecia more exact information about when normal regrowth of hair will occur. From the time a hair is lost from the scalp, approximately four and three-tenths months will elapse before the follicle has regenerated so that it can begin to produce a new hair. The rate of growth (0.35 mm. a day) is such that approximately another six months will elapse before the hair itself reaches its maximum growth. This explains why it takes a patient with an alopecia, such as alopecia areata, of the scalp at least nine months to achieve a normal regrowth of hair. Such data are available for all types of human hair (axilla, thigh, chin, eyebrow and so forth). The life span of a human scalp hair is approximately two years; that of an eyelash is three months, and that of an eyebrow is three weeks. Such information also makes it possible for the clinician

to know the exact duration of hair loss if he sees new hair growing. In this way a more exact history can be elicited from the patient. The implications of the effectiveness of any therapy for any specific hair loss are obvious.

Sebaceous Glands

Since the apocrine gland, hair follicle and sebaceous glands are derived from the same embryonal germ layer it is difficult to discuss one and not the others. They are all closely related from the standpoint of growth, development and interplay of function. Unlike the sweat gland the sebaceous gland does not depend on the autonomic nervous system for its activity. The ability of a sebaceous gland to produce sebum is directly correlated with its size. A large gland secretes a good deal of fat, a small one only a little. The size and, therefore, the activity of the sebaceous gland can be increased with androgen stimulation, and, contrariwise, estrogens will make an oil gland small. This information is utilized in the treatment of skin diseases associated with an increase in oil-gland size and therefore activity, such as acne vulgaris, seborrhea and even the tumors of senile sebaceous adenoma.[17] Estrogens may be used in the treatment of acne vulgaris in the female to regulate an abnormal menstrual cycle. Recently, an opportunity presented itself to treat the large tumors of sebaceous adenoma with systemic estrogens alone, with a resultant melting away of such tumors.[17]

The accumulation of sebum on the surface of the skin is largely controlled by the viscosity of the surface fats and is thus altered by temperature; the lower the temperature, the less fluid the sebum. This lowered viscosity largely affords resistance to further flow of sebum from the gland opening, in one way regulating the accumulation of oil on the surface of the skin. If the surface fat of the skin is removed, as in frequent washings with soap and water, the stored fat in the sebaceous gland then flows to the surface, giving an apparently rapid rate of secretion. The clinician, at this point, might question the advisability of such cleansing in the treatment of seborrhea or acne. However, depletion of the stored fat in the gland soon occurs and is accompanied by a decreasing rate in flow, which then falls to the level of continuous rate of fat formation by that gland. It is not until this phase is reached that the clinician can estimate the true base line of seborrhea for any given patient.

The amount of fat, then, on any given area of skin is a result of, first, the number of sebaceous glands, which cannot be altered pharmacologically but can be destroyed by local destructive measures such as electrolysis; secondly, the size of the sebaceous glands and therefore the amount of fat formation that can be altered with estrogens; thirdly, the rate of fat flow from the gland, which can be altered by temperature (viscosity) and washing; and, finally, the rate of fat spread over the surface of the skin, which is dependent on the wetness of the surface.

When one thinks of oils and lubricants one naturally thinks of the treatment of the dry skin. Whether the dry skin is the result of simple chapping or of an inflammatory dermatosis, the treatment problem is the same. Perhaps the greatest fundamental contribution to topical therapy in recent years has been made by Blank,[18] who has demonstrated that a dry skin is not one without adequate oil but one without adequate water. The effect, then, of any topically applied oil is to prevent the evaporation of water from the surface cells (stratum corneum). When the relative humidity of the atmosphere falls below 50 per cent, water will evaporate from the surface of the skin faster than it can be replaced by diffusion from the deeper tissue. To treat properly any skin that is flaky and rough, less flexible or fissured one must first soak the part in tap water, preferably at skin temperature, to hydrate the stratum corneum. During this hydration procedure the roughness, flakiness and inflexible quality of the dry skin is lost. As soon as an adequate hydration is complete, a film of hydrophobic lubricant such as plain, white petrolatum must be applied while the skin is still wet. In the extensively desquamating and fissuring phase of any dermatosis (acute or chronic) such a procedure may need to be repeated three or four times in a twenty-four-hour period; this is especially so in the winter months in New England when the atmospheric humidity is low and the hydration of skin from active temperature-regulating sweating is also apt to be low. During the hot, humid summer months, the intensity of the "hydration-lubrication" therapy can be lessened.

Sensation

The one sensation associated exclusively with the skin and cutaneous disease and with no other internal structures of the body, of course, is that of itching.[19] Itching, which has been defined as "an unpleasant cutaneous reaction which provokes the desire to scratch,"[20] is a function of the epidermis just beneath which the terminal nerve endings are located. No itching is present when the epidermis is denuded. In recent years the physiology of itching has been better understood. Itching is "weak pain." It is mediated by pain receptors and pain fibers and occurs when the pain receptors are weakly stimulated. When, with local anesthetics, the perception of pain disappears, itching also disappears; itching returns with the return of pain perception. This has also been observed clinically in diseases with sensory disassociation such as syringomyelia and leprosy. In other words itch is present only when pain is present.

Itch sensation can be separated into components[21]: one is the spontaneous itch or a prickling itch sen-

sation, which occurs as "itch spots" in all normal persons or can be produced locally by many pathologic processes (dermatitis, histamine wheal, heat, insect bites and so forth). It is of short duration and well localized and disappears in a few minutes, particularly if the area is not scratched. It is suggested that spontaneous itch is a function of the myelinated fibers of the cutaneous nervous system. This spontaneous itch sets the stage for the second type, called itchy skin, which is of long duration, enduring for hours or days. It is thought to be a function of the unmyelinated cutaneous nerve endings. The itchy skin surrounds the site of spontaneous itch like a halo and is poorly localized. It can be initiated by a light touch, pressure, cold or heat. Certainly, if the dermatologic disease did not itch, therapeutic problems and management of the patient would be far simpler. If a scratch is made through the halo of itchy skin, it immediately changes to intense "pricking itch," which in turn develops another, wider halo of mild itch around it. Extension of the scratch repeats this process. The normal response to the scratch, then, is for the itch sensation to spread out in waves from the initial site. As the scratch spreads with the itching it is not uncommon for the entire body to be engulfed in this most unpleasant sensation.

Scratching is a normal reflex response to the itch sensation, and the patient should not be criticized or condemned for scratching any more than one should criticize the patient with hay fever for sneezing. This intolerable weak pain called itch is so unpleasant that one tries to convert it to strong pain, which can be endured. For the same reason one bites on a toothache or massages an aching muscle to make it hurt more; one scratches an itch to convert the weak pain of itching to strong pain. Scratching, thus, will relieve itch by stimulation of pain endings or by completely removing the nerve endings with one's fingernails or by breaking up the monotony of the nerve-fiber response producing the itch. To accomplish this pain conversion the skin must obviously be injured. The skin, in turn, must protect itself against any acute or chronic injury. This protective response on the part of the skin is a rapid, dramatic[22] increase of mitotic activity (preceded by the necessary chemical responses to furnish energy for that activity), with a resultant thickening of the epidermis and exaggeration of the normal skin lines. This, of course, is called lichenification.

It is important to understand, on any itching patient, the exact cause or causes for his pruritus at any given time. For example whealing or urticarial lesions of the skin can itch diffusely on either a histaminic or a cholinergic basis; the retention of sweat as a primary or complicating disease in any dermatosis produces a pricking or burning type of itch; the roughness, dryness or flakiness of a dry skin produces poorly localizable, diffuse, itchy skin; active allergic eczematization causes both types of itch.

Since itch is a part of pain, control of itching should be as exact a science as the control of pain. It has been shown that none of the local anesthetics or antihistaminics when applied locally penetrate the intact normal or injured skin sufficiently to alter the pain on its threshold.[23,24] Fifty-four topical antipruritic preparations commonly prescribed were found to have no effect on experimentally produced histamine pruritus in man.[25] However, anything that cools the surface of the skin will stop the itch, and, contrariwise, anything that usually warms or flushes the skin will enhance the itching sensation. But, as in the weak pain of toothache, headache or muscle ache, the internal medication of greatest value in holding down the intensity of the sensation of itching is the salicylate group. In other words aspirin is still the best anodyne and the best anti-itch drug.[26]

Conclusions

The physiology of the skin has received much attention in recent years. The practice of modern dermatology encompasses such applied physiology of the skin. Unfortunately, the limited time allows the presentation of only a few such clinical applications of skin physiology in the understanding of a patient's problems. It has been impossible even to mention biochemical aspects of cutaneous disease. On the basis of such fundamental knowledge in the field of physiology, chemistry and immunology new concepts of etiology as well as of diagnosis and treatment are being introduced into the field; many of the old empiricisms are at last being rationally understood and more deeply rooted in the diagnostic and therapeutic armamentarium.

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SCREENING FOR CARDIOVASCULAR DISEASE IN A COMMUNITY

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TO discover persons with a high probability of cardiovascular disease and refer them to their physicians for diagnosis and treatment, a case-finding program was started in Newton, Massachusetts, in July, 1949. This report summarizes the experience and results of screening in 15 groups totaling approximately 8000 persons from July, 1949, to March, 1952.

Case finding was one portion of a general community heart project established jointly by the Newton Health Department, the Massachusetts Department of Public Health and the United States Public Health Service to determine what a community can do about its heart-disease problems. The complete program, as reviewed elsewhere,[1] included a postgraduate lecture series in heart disease for physicians; a program for prevention of rheumatic fever[2,3]; the development of a low-sodium-diet education project[4]; refresher courses for technicians in prothrombin determinations; cardiac nursing services; weight guidance for overweight persons by the group method; and a plan for the prevention of subacute bacterial endocarditis. Planning and development of the heart program was under the guidance of the Cardiac Program Committee, a group of 6 practicing physicians from the staff of Newton–Wellesley Hospital appointed by the Newton Medical Club.

A subcommittee on case finding, consisting of 3 practicing physicians, was appointed by the Cardiac Program Committee to determine what might be done to get patients with heart disease to their physicians for medical supervision. The presence of the Heart Program in the community for a year and the cardiac lecture series had made the physicians more aware of the problems of heart disease. Any person referred for suspected heart disease could expect to receive a careful evaluation to determine the nature and importance of the condition. The problem for the subcommittee was to devise and plan a practicable heart-disease screening program and yet to avoid creating cardiac neuroses.

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METHOD

Screening Procedures

It was believed that the screening should be limited to persons eighteen years of age and over, since the school examinations covered most children through their high-school years. The types of abnormalities that the screening aimed to detect were primarily rheumatic, hypertensive and coronary-artery disease although the importance of discovering patients with congenital, syphilitic or thyrotoxic heart disease was recognized. Uncomplicated, mild hypertension was not considered a reason for referral; however, there were several different views about what constituted mild hypertension.

The screening procedure decided on by the Subcommittee on Case Finding and approved by the Cardiac Program Committee consisted of the following tests: a six-question, self-answered history questionnaire, determination of the blood pressure and auscultation of the heart.

Any person who was already under the care of a physician for heart disease was not eligible for the screening. The history questions were to ascertain whether the subject had knowledge of an underlying cardiovascular disorder or had symptoms of possible cardiac origin. The self-answered questionnaire was later reviewed by the screening physician, who evaluated the significance of the positive answers.

Height and weight were recorded by a Red Cross volunteer to provide an estimate of the obesity problem in the community.

The blood pressure was taken by a public-health nurse according to the newer recommendations for blood-pressure determinations of the American Heart Association,[5] and was retaken by the physician if the results were in a range in which there was a question of referral.

Auscultation of the heart was done in screened examining booths by public-health physicians who were not cardiologists but were of the level of medical residents with special interest in cardiovascular disease. Men were examined stripped to the waist; women were given hospital gowns to wear during examination. Auscultation was performed with the person lying on the examining table and then in the sitting position. Examination in the left lateral decubitus position was also done when there was a question of a mitral diastolic murmur or a history of rheumatic fever.

The subject was not given any information of findings but was told that a report would be mailed to him within a few weeks. On leaving he was given a folder that further explained the purpose of the screening and the method of reporting. The average time required for the entire procedure was fifteen minutes; the average physician time for each person was four minutes, with more time as needed for any who presented some suspected findings in the history or on examination.

Referral System

Cardiovascular disease was suspected if one of the following findings was present:

A history of chest discomfort suggestive of angina pectoris or a previous history of a "heart attack"; a history of dyspnea on exertion not obviously attributable to obesity, asthma or emphysema; a history of paroxysmal nocturnal dyspnea, orthopnea or one suggestive of congestive heart failure; or a history of rheumatic fever or chorea in the presence of a heart murmur.

A blood-pressure reading (lowest) of 160 systolic, 96 diastolic, or higher (young male subjects with a reading of 140 systolic, 90 diastolic, or higher were also reported to the private physician for decision regarding referral).

A systolic murmur of Grade 3 or greater, using the grading system of 1-6 of Levine and Harvey[6] (at the beginning rough Grade 2 systolic murmurs were considered suspicious of organic disease, but so few of the private physicians regarded them as significant that Grade 3 was decided on for referral except in persons with a history of rheumatic fever who also had a Grade 2 mitral systolic murmur); any diastolic murmur; or frequent extrasystoles or other significant abnormalities of rhythm.

Several factors were considered in the development of the referral system. Many persons had some elevation of blood pressure or a murmur that the private physician either knew about or did not consider significant. Likewise, some physicians did not want their patients to know that they had hypertension or heart disease and maintained periodic medical supervision under some other guise. It was believed that the reports to the subject should not be phrased to alarm him and, if negative, should not give him a false sense of security. The referral system was evolved in an effort to meet these problems.

If the person being screened had findings suggestive of cardiovascular disease a report of these findings was mailed to the private physician on the day after the screening. The physician was asked to review the findings and indicate, on a coded post card mailed back to the health department within ten days, whether or not he wished the patient referred to him for further examination. It was soon learned that the physicians who had not replied within ten days usually wished to have the person referred for further evaluation but had not had time to return the card. The procedure was thus modified so that the physician returned the card only if he did not wish to see the patient.

Reports to the subjects were held for two weeks to allow time for the physicians to indicate which persons they did not want referred. If the findings caused no suspicion of heart disease the person being screened was sent a negative report. If he was to be referred to his physician for further examination he received a letter advising him to report to his physician. If he had suspicious findings but his physician did not want him to be referred he was sent a letter telling him that his screening findings had been reported to his physician, who did not consider further examination required at that time.

To get a report on the findings of the patients referred, letters were sent to the physicians a month later, asking them to indicate on return post cards whether or not the patients had reported to them and the results of the examination.

Results

Community Participation

Results of a pilot study in which 270 municipal and industrial employees were screened led the Case Finding Subcommittee to ask the Newton Community Council to carry on a community-wide heart-disease screening program. The Council, a central planning agency in the fields of health, social service, recreation and education, represents about 80 Newton organizations as well as members-at-large. The Council's governing board set up a representative heart committee to take responsibility for stimulating public participation in the screening program.

Since Newton's population of about 80,000 is divided into 14 separate villages, the Heart Committee decided to approach the community screening program on a village-by-village basis. Members of the

Heart Committee helped representatives of the villages decide whether or not to conduct a screening program, helped them find leaders to serve on village heart-disease screening committees and provided guidance in program planning.

TABLE 1. *Results of Screening and Confirmation among Male Employee Groups according to Age.*

Outcome of Screening & Referral	Totals		Under 30 Yr. of Age		30-39 Yr. of Age		40-49 Yr. of Age		50-59 Yr. of Age		Over 60 Yr. of Age		Age Unknown	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
Totals screened	1693		394		461		370		303		161		4	
Suspected	359	21.2	62	15.7	74	16.1	62	16.8	101	33.3	60	37.3		
Routine positive findings	278	16.4	46	11.7	61	13.2	47	12.7	78	25.7	46	28.6		
Reported	171	10.1	23	5.8	38	8.2	33	8.9	46	15.2	31	19.3		
Confirmed	78	4.6	7	1.8	11	2.4	18	4.9	21	6.9	21	13.0		
No previous history	52	3.1	3	0.8	7	1.5	13	3.5	14	4.6	15	9.3		

Response to Screening

Several industries were first approached to determine whether management was interested in having the screening offered to employees. Most of the employers were interested in having the screening, provided that it would not require too much loss of time for the employees or disruption of production. If the employer was interested and could arrange for suitable facilities a meeting was held with representatives of the employees to explain the purpose of the screening, its potential benefits and its limitations. When possible a group meeting with the employees was held to explain the program and answer questions, since an immediate concern of the workers was whether management would have access to the findings and possibly use them as reason for dismissal. After learning that the results were confidential and would be given only to the personal physician named by the employee, they readily accepted the idea of the heart screening. Response of the workers to the offer of screening was quite good: 4000, representing 77 per cent of the eligible employees of the eight institutions and industries, were screened.

TABLE 2. *Results of Screening and Confirmation among Males in the General Population according to Age.*

Outcome of Screening & Referral	Totals		Under 30 Yr. of Age		30-39 Yr. of Age		40-49 Yr. of Age		50-59 Yr. of Age		Over 60 Yr. of Age		Age Unknown	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
Total screened	1091		211		320		258		168		134			
Suspected	167	15.3	24	11.4	31	10.0	36	14.0	36	21.4	40	29.9		
Routine positive findings	107	9.8	17	8.1	21	6.6	24	9.3	25	14.9	20	14.9		
Reported	83	7.6	14	6.6	17	5.3	18	7.0	18	10.7	16	11.9		
Confirmed	31	2.8	1	0.5	3	0.9	8	3.1	10	6.0	9	6.7		
No previous history	21	1.9	1	0.5	3	0.9	5	1.9	8	4.8	4	3.0		

Heart-disease screening in the industries was a convenient and relatively easy procedure. However, this was a restricted group, and it was wondered what results would be obtained by offering the procedure to the general adult public. A great deal of organizational work was done by the Heart Committee and local village committees to inform the public about the screening program and make appointments for the screening. The physician Subcommittee on Case

TABLE 3. *Results of Screening and Confirmation among Female Employee Groups according to Age.*

Outcome of Screening & Referral	Totals		Under 30 Yr. of Age		30-39 Yr. of Age		40-49 Yr. of Age		50-59 Yr. of Age		Over 60 Yr. of Age		Age Unknown	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
Total screened	2277		1142		626		303		153		46		7	
Suspected	350	15.4	129	11.3	84	13.4	59	19.5	56	36.6	22	47.8		
Routine positive findings	250	11.0	107	9.4	68	10.9	39	12.9	28	18.3	8	17.4		
Reported	133	5.8	44	3.9	44	7.0	21	6.9	18	11.8	6	13.0		
Confirmed	47	2.1	6	0.5	15	2.4	10	3.3	12	7.8	4	8.7		
No previous history	29	1.3	3	0.3	9	1.4	7	2.3	8	5.2	2	4.3		

Finding and the Cardiac Program Committee passed on the type of publicity material that would be used.

In the 7 village groups that were offered the screening 3739 persons were screened, representing an average of 19 per cent of the eligible population. Several factors can account for the greater participation by the industrial groups, but the convenience of having the procedure right at the place of employment during working hours was probably important. Likewise, the group psychology of participation is stronger in such a situation. Screening in the villages was on an appointment basis and required the subject to travel to the screening center from his home, or to take time off from his work. Probably the same inertia that keeps many well intentioned people from going to their physicians for routine physical examinations was present here.

TABLE 4. *Results of Screening and Confirmation among Females in the General Population according to Age.*

Outcome of Screening & Referral	Totals		Under 30 Yr. of Age		30-39 Yr. of Age		40-49 Yr. of Age		50-59 Yr. of Age		Over 60 Yr. of Age		Age Unknown	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
Total screened	1697		388		402		414		304		188		1	
Suspected	291	17.1	29	7.5	28	7.0	53	12.8	93	30.6	87	46.3	1	100.0
Routine positive findings	210	12.4	23	5.9	22	5.5	39	9.4	67	22.0	59	31.4		
Reported	174	10.3	18	4.6	18	4.5	34	8.2	55	18.1	49	26.1		
Confirmed	94	5.5	8	2.1	6	1.5	10	2.4	36	11.8	34	18.1		
No previous history	44	2.6	8	2.1	6	1.5	5	1.2	13	4.3	12	6.4		

Follow-up Response

Of the first 566 persons who received positive reports and about whom follow-up information was obtained 488, or 80 per cent, were known to have gone to their physicians within three months of the screening examination. The health department sent letters to these 566 patients urging them to consult their own physicians for further examination or advice. Three hundred and fifty, or 62 per cent, of those referred, took this action after receiving the letter. Of the 216 who did not respond to the letter 172, or 80 per cent, were visited or telephoned by a public-health nurse. Ninety-eight, or 57 per cent, of those with whom the nurses communicated went to their physicians within the three-month period.

Cases Found

The records of the first 6758 persons screened were used for an analysis of yield. This represented 8 special employee groups totaling 3970 persons and 6 general population groups totaling 2788 individuals (Tables 1-4).

Of the 6758 screened 1167 (17.3 per cent) were suspected of having cardiovascular disease.

The personal physicians requested referral of 845 of the 1167. In the remaining 322 the physicians requested that no referral be made because the findings were not considered significant or the patient was known to have cardiovascular disease.

At least 561 of the 845 patients referred were definitely seen by their physicians. Information on 284 of the 845 referred for suspected disease is lacking because the patient did not report or no reply was received from the physician. It was later learned that some of these persons reported to a different physician than the one originally listed.

In 250 (45 per cent) of the 561 who reported, cardiovascular disease was confirmed by the physicians' re-examination.

In 408 of the 1167 suspected cases cardiovascular disease was verified either through subsequent examination or from previous knowledge of existence of the disease by the personal physician. This represented a confirmation rate of 36 per cent of those suspected, or 6 per cent of the base population screened. In the special employee group it was 5 per cent, and in the general population group it was 7 per cent.

An additional 76 cases (1.1 per cent of those screened) were found on examination by the physicians to warrant further study for possible heart disease.

TABLE 5. *Diagnoses Reported in 250 Cases Confirmed by Examination in Persons Reporting.*

Diagnosis	Totals	Previous History	No Previous History
		No. of cases	No. of cases
Rheumatic heart disease	49	14	35
Hypertension	96	45	51
Hypertensive heart disease	66	34	32
Arteriosclerotic heart disease	36	14	22
Other	18	4	14
Totals	265	111	154

Of the 250 persons with cardiovascular disease confirmed by subsequent examination by their physicians, 146 (2 per cent of the base population) had given no history of cardiovascular disease at the time of screening, and 104 (1.7 per cent of the base population) had given a history of cardiovascular disease at the time of screening (Table 5).

Since the private physician determined whether the person suspected of having cardiovascular disease should be referred it is of interest to analyze the reasons given for not desiring referral. For about 85 per cent of the 322 who received a "modified positive" report the physician gave a reason for not wishing to see the patient. Almost 60 per cent (158 persons) of the 273 with such a reason given were already known to have a cardiovascular disease and presumably required no further evaluation. The remaining 42.1 per cent (115 persons) had screening findings that were not considered significant by the physician; analysis revealed that no one who needed treatment was denied referral. An arbitrary system of referral for all persons suspected of having cardiovascular disease would have resulted in the sending of 27 per cent of the suspected groups to their physicians without the physicians' wish for such a referral. Undoubtedly, having the personal physicians determine whether or not referral was warranted helped to prevent ill feeling that could have resulted from unnecessary referrals.

Opinions of the Physicians

Two hundred and thirty-seven physicians were referred 561 patients, who definitely reported for a further examination for cardiovascular disease. It is unknown how many of the remaining 284 also finally reported. Most of the physicians saw between 1 and 5 patients. Twenty-six of these physicians participated on various committees concerned with the Newton Heart Demonstration Program.

At the conclusion of the screening program in 1952, 28 physicians of the 135 practicing in Newton were interviewed by a person not connected with the program to determine their reactions to the screening. This independent researcher selected a sample consisting of 3 groups of physicians: those who had no patients referred; those with a medium number of referrals (7-15); and those with a larger number of referrals. Of the 28 physicians interviewed 22 expressed opinions favorable to the program, 4 seemed to have unfavorable opinions, and 2 were in doubt and could not express an opinion.

The co-operation of the physicians was excellent. Of the first 582 positive referrals the physicians returned reports on 97 per cent, either stating the diagnosis or telling that the patient had not yet reported for examination. Several of these physicians lived outside Newton and knew little about the program.

Cost of Screening

The cost of screening differed considerably between the industrial groups and the village groups. Among the most important reasons for the difference was the more efficient scheduling of persons that kept the screening team fully occupied during the hours of screening.

An estimate of the costs during the operating phase of one industrial screening was made. Approximately 2000 persons were given the heart screening at a rate of 110 to 130 in a five-hour day. The personnel in the screening team consisted of 2 physicians, 2 nurses and 3 volunteers. The estimated cost per person screened for the operating phase — that is, all costs from the time the subject appeared at the screening site until the time that both he and his physician received a report of the screening — was $0.45. Incidentally, this group of employees also had the 70-mm. x-ray film of the chest, which was arranged as a combined procedure with the Massachusetts Department of Public Health and the Newton Tuberculosis and Health Association.

A detailed study was done in a village in which 951 persons received the heart screening. The comparable operating-phase cost of this village screening was $1.12 per subject; however, only 45 persons were screened each day as compared with the possible rate of 120 as in the industrial screening. The operating phase of the screening represented the major expense of the program. However, time spent by paid personnel in helping the community organize for the screening and extra follow-up procedures by public-health nurses would also have to be included.

Discussion

Some of the problems of case finding for cardiovascular disease in a general community were explored over a three-year period as one phase of a total community heart program. The purpose of the case finding was to obtain the benefits of early recognition and medical supervision for patients with cardiovascular disease and yet to avoid the potential danger of creating cardiac neuroses. A voluntary case-finding procedure based on a brief cardiac history, the recording of blood pressure and auscultation of the heart was carried out on about 8000 adults representing employee and general-population groups.

The screening procedure employed in this study proved to be most effective when used in industrial groups rather than in the general-population groups. Organizing an industrial screening was relatively easy when management was co-operative and proper facilities were available.

Organizing a village screening brought many persons into active participation in the screening program and probably had a broader health-education effect; however, the difficulties of such an approach made this type of screening less practicable. The educational effect of the program is difficult to assess, and no attempt was made to evaluate this aspect of the program.

Approximately 17 per cent of the adults screened had some suspected cardiovascular condition according to the criteria used. When these findings were reported to the personal physicians, the physicians requested that three fourths of this group be referred for further study. They did not wish to see the remaining 25 per cent because their findings were already known or were not considered significant.

In 45 per cent of the 561 patients who reported to their physicians for further examination the suspicion of cardiovascular disease was confirmed. This represented 3.7 per cent of the base population. Over half this number, or 2 per cent of those screened, stated that they had no previous knowledge of cardiovascular disease. The remainder of the confirmed cases were previously known but not under medical supervision for the condition.

The attitude of the public toward the screening was mostly to regard it as a "matter-of-fact" health measure. The lack of spectacular devices to attract the curiosity seekers disappointed some persons, but it was hoped that application of the familiar procedures of the doctor's office would emphasize the value of the periodic checkup.

The practicing physicians helped to plan the program from the start, and as a result the project that evolved was accepted and supported by the majority of the medical profession in the community.

Summary

A case-finding program for cardiovascular disease was carried out over a period of three years as part of a total community heart program. The method of case finding in this pilot study and the approach to the public were planned with the help of practicing physicians and with a heart committee of citizens from the community. An effort was made to encourage a common-sense attitude toward maintaining health by urging a periodic checkup to detect conditions that could lead to "heart trouble." An attitude of optimism was stressed regarding the outlook for preventing some forms of heart disease and for preventing "heart trouble" when heart conditions already existed.

A screening procedure based on a brief cardiac history, the recording of blood pressure and auscultation of the heart was offered on a voluntary basis to employee groups and later to the general public. Approximately 8000 adults were screened by this method, which yielded 17 per cent suspected positive findings for cardiovascular disease. The personal physicians to whom the suspected findings were reported believed that 11 per cent of the total screened had findings that warranted further examination to establish or rule out cardiovascular disease. In 45 per cent of those who reported for re-examination the presence of cardiovascular disease was confirmed.

Although 6 per cent of the base population screened were found to have cardiovascular disease, in slightly over a third of this group (2.3 per cent), the personal physician knew of the findings and did not request referral. Of the 3.7 per cent with cardiovascular disease in the group in which referral was requested over half, or 2 per cent, gave no history of cardiovascular disease at the time of screening.

This report is not intended as a recommendation of this particular procedure for case finding in cardiovascular disease. It is presented to help visualize some of the problems that can be expected in the practical application of any mass case-finding procedure for cardiovascular disease.

We are indebted to Drs. Stephen D. Peabody and Thomas E. Chretien, members of the Subcommittee on Case Finding; to Dr. Egon E. Kattwinkel, chairman of the Cardiac Program Committee, and to the Cardiac Program Committee members, who freely gave many hours of their time in the guidance of the program; to Dr. Lewis C. Robbins, whose efforts laid the groundwork for the program; to Dr. William Kannel, who helped with the screening examinations; to the nurses and other staff members of the Newton Health Department and Newton Heart Demonstration Program; to Mrs. Meyer Armet, Mrs. Eugenia Copeland and many other persons and organizations in the community who contributed to the screening program in many ways; and, finally, to the Program Analysis Section, Division of Chronic Disease and Tuberculosis, Public Health Service, for tabulating and analyzing the data in this study.

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CANCER OF THE CERVIX IN JEWISH WOMEN*

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BOSTON

CONSPICUOUS in the demography of cancer is the infrequency of cancer of the cervix in Jewish women. Kennaway,[1] in 1948, carefully summarized all the available reports relevant to this observation, pointing out that many of the early surveys did not distinguish cancer of the cervix from cancer of the corpus uteri. Review of these reports shows that many of them, including the more recent ones, fail to furnish evidence that the diagnoses were confirmed by the customary routine methods of pathological examination of excised tissue. Other data

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that were lacking made accurate assessment of the question impossible. Since Kennaway's report a few additional observations have been made. Gusberg and Corscaden[2] stated that of a series of 999 cases of squamous carcinoma of the cervix 3 cases occurred in Jewish women, or 1:333, whereas in a series of 48 cases of adenocarcinoma of the cervix 6 cases occurred in Jewish women, or 1:8. Weiner, Burke and Goldberger[3] found that carcinoma of the cervix was five and a third times more frequent in non-Jewish than in Jewish women. Scapier, Day and Durfee[4] observed that intraepithelial carcinoma of the cervix was six times more frequent in non-Jewish than in Jewish women.

TABLE 1. *Histologic Types of Cancer of the Cervix in Jewish and Non-Jewish Women at the Beth Israel Hospital, Boston (1928-1953).*

HISTOLOGIC TYPE	JEWISH PATIENTS	NON-JEWISH PATIENTS
Invasive squamous carcinoma	16	50
Invasive squamous carcinoma plus adenocarcinoma in situ	1	0
Adenocarcinoma	2	0
Adenoacanthoma	0	1
Carcinoma, unclassified, q.n.s.	0	1
Total invasive carcinomas	19	52
Squamous carcinoma in situ, with gland involvement	1	3
Squamous carcinoma in situ, surface	1	0
Leiomyosarcoma	1	0
Mixed mesodermal tumor	0	1
Total cancers of cervix	22	56

CARCINOMA OF THE CERVIX

The present report is based on all women admitted to the Beth Israel Hospital, Boston, from August 20, 1928, to December 31, 1953, in whom the diagnosis of cancer of the cervix was verified by histologic evidence. The original histologic slides were reviewed by us independently. The cases classified as cancer in this report were accepted by both of us; in none of the cases reviewed was there any disagreement regarding the benign or malignant nature of the lesion. We have excluded 3 cases of advanced adenocarcinoma involving both the endocervix and the endometrium in which primary endocervical origin could not be established and 1 case in which the biopsy material had been lost. In these 4 excluded cases 2 patients were Jewish.

During the period studied 86,214 women were admitted to the Beth Israel Hospital. Of these, 66,226 (76.7 per cent) were Jewish according to data (23.3 per cent) were not Jewish according to data furnished by patients on admission and confirmed by internal evidence in their records and from social-service notes. In the entire group 78 patients with cancer of the cervix of various histologic types were found (Table 1). Of these, 22 cases (28.2 per cent) occurred in the Jewish women, a rate of 33.2 per 100,000 female hospital admissions, and 56 cases (71.8 per cent) were found in the non-Jewish women, a rate of 280 per 100,000. The 22 Jewish patients ranged in age from twenty-seven to seventy-four years, with a mean age of forty-eight years, and the 56 non-Jewish patients from thirty-one to seventy-four, with a mean age of fifty years. In this series all 22 Jewish women were married, 1 being nulliparous. In the non-Jewish group 55 women were married and parous; 1 woman was single.* Eliminating 2 cases of squamous carcinoma in situ in Jewish women, 3 similar cases in non-Jewish women, 1 case of leiomyosarcoma in a Jewish woman and 1 case of mixed mesodermal tumor in a non-Jewish woman (Table 1), these data read as follows: 19 (26.7 per cent) invasive carcinomas in Jewish women, a rate of 28.7 per 100,000; and 52 (73.3 per cent) invasive carcinomas in non-Jewish women, a rate of 260 per 100,000. This correction is made so that these figures will be comparable to those furnished by other Boston hospitals in which carcinomas in situ and sarcomas were eliminated, only invasive carcinoma of the cervix being included. These and other comparative data are summarized in Table 2. In either event the ratio of carcinoma of the cervix in Jewish to non-Jewish women is, thus, approximately 1:9. From the rates mentioned above and from this ratio it can be calculated that if a given female population contains 5 per cent Jewish women, 1 out of every 170 cases of cervical carcinoma will occur in a Jewish woman.

TABLE 2. *Cancer of the Cervix in Jewish and Non-Jewish Women and in Divers Local Populations.*

SOURCE	TOTAL ENUMERATION	ALL CANCERS OF CERVIX	INVASIVE CARCINOMAS	RATE*
				per 100,000
Beth Israel Hospital (1928-1953)				
Total women admitted	86,214	78†	71†	82.4
Jewish women	66,226	22†	19†	28.7
Non-Jewish women	19,988	56†	52†	260.0
Peter Bent Brigham Hospital (1928-1953)	136,400 est.	—	202†	148.0
Massachusetts General Hospital (1927-1953)	204,073	—	1058†	518.0
Free Hospital for Women (1926-1947)	49,909	1186†‡	1183†	2372.0
Commonwealth of Massachusetts (1952)				
Prevalence	2,461,327		1433	58.3
Incidence	2,461,327		623	25.3

*Computed on basis of invasive carcinoma.
†All cases histologically confirmed.
‡Includes sarcomas but not carcinomas in situ.

*The age of these women at marriage and their age at primiparity were not ascertainable. Data relevant to socioeconomic status, such as occupation of husbands, are undetermined.

Carcinoma of the Corpus Uteri

To compare the frequency of carcinoma of the cervix with carcinoma of the corpus uteri, a search was made of material in the files of the Department of Pathology at the Beth Israel Hospital. The interval studied and the hospital population were the same as those for the cervix. Only cases in which there was histologic confirmation of the diagnosis were included. Among the 86,214 women admitted 114 cases of cancer of the corpus uteri were found, a total rate of 132 per 100,000. Of these, 85 (74.6 per cent) occurred in Jewish women, a rate of 128 per 100,000, and 29 (25.4 per cent) in non-Jewish women, a rate of 145 per 100,000. The 85 Jewish women ranged in age from thirty-one to eighty-seven years, with a mean age of fifty-eight years; the non-Jewish women ranged in age from thirty-eight to seventy-nine years, with a mean age of fifty-seven years. The histologic classification of these tumors is given in Table 3. If, as in the data on carcinoma of the cervix, sarcomas and noninvasive carcinomas are excluded, the data read as follows: 74 (72.5 per cent) invasive carcinomas in Jewish women, or a rate of 112 per 100,000, and 28 (27.5 per cent) invasive carcinomas in non-Jewish women, or a rate of 140 per 100,000 (Table 4). There does not appear to be any significant difference in the rates per 100,000 women of the respective groups. The ratio of carcinoma of the corpus uteri in Jewish women to non-Jewish women is, thus, 1:1.25. The contrast between carcinoma of the corpus uteri and that of the cervix in this regard is shown in Table 4.

Table 3. *Histologic Types of Cancer of the Corpus Uteri in Jewish and Non-Jewish Women at the Beth Israel Hospital, Boston (1928-1953).*

Histologic Type	Jewish Patients	Non-Jewish Patients
Adenocarcinoma	66	23
Adenoacanthoma	4	2
Undifferentiated carcinoma	4	3
Total invasive carcinomas	74	28
Adenocarcinoma in situ	2	1
Adenocarcinoma in polyp	1	0
Leiomyosarcoma	5	0
Endometrial stromal sarcoma	1	0
Carcinosarcoma	2	0
Total cancers of corpus	85	29

Discussion

The proportion of carcinoma of the cervix and carcinoma of the corpus in relation to the total of uterine carcinomas reflects the distribution of the two lesions in Jewish and non-Jewish women. With the rates per 100,000 as a basis of computation, the ratio of carcinoma of the cervix to carcinoma of the corpus uteri in Jewish women is 1:4, whereas that in non-Jewish women is 2:1. Data from the Massachusetts Department of Public Health* indicate that in 1952 both the prevalence and the incidence† of cancer of the cervix in relation to cancer of the corpus uteri for the female population of the Commonwealth were approximately 5:1. The comparison between the data from the Beth Israel Hospital and those from the Commonwealth is shown in Table 5.

Rates as given vary not only with the nature of the hospital population but also with the internal organization of the hospital (Table 2). As an example, 204,073 women were admitted to the Massachusetts General Hospital from 1927 to 1953, of whom 1121 had primary invasive carcinoma of the cervix, a rate of 549 per 100,000. Histologic confirmation was lacking in 63 of these cases. The prevalence rate for histologically confirmed cases was 518 per 100,000.‡ In contrast, only 202 patients with invasive carcinoma of the cervix were found in an estimated 136,000 female admissions (repeat admissions not excluded) at the Peter Bent Brigham Hospital from 1928 to 1953, a rate of 148 per 100,000, the number being that indexed as cervical carcinoma in the Pathology Department.§ The effect of the organization of a hospital on the frequency is seen at its maximum at the Free Hos-

Table 4. *Distribution of Hospital Admissions and Uterine Carcinomas in Jewish As Compared with Non-Jewish Women (1928-1953).*

Datum	Totals	Jewish Patients			Non-Jewish Patients		
		No.	Percentage	Rate	No.	Percentage	Rate
				per 100,000			*per 100,000*
Hospital admissions, female	86,214	66,226	76.7	—	19,988	23.3	—
Uterine carcinomas, total	173	93	53.8	140	80	46.2	400
Invasive carcinoma, of corpus	102	74	72.5	112	28	27.5	140
Invasive carcinoma, of cervix	71	19	26.7	28.7	52	73.3	260

*Data kindly furnished by Dr. Herbert L. Lombard.

†Prevalence is defined as the total number (census) of cases of a given disease in a population at any one time. Incidence is defined as the number of new cases of that disease arising in the same population during a unit of time.

‡Data kindly furnished by Dr. John B. Graham.

§Data kindly furnished by Dr. Gustave J. Dammin.

pital for Women, a 91-bed hospital devoted exclusively to gynecology, where 49,909 patients were admitted from 1926 to 1947 and 1183 cases of histologically confirmed invasive carcinoma of the cervix were found, a rate of 2372 per 100,000.* The difference in rates between the Massachusetts General Hospital and the Peter Bent Brigham Hospital is interpreted as a reflection of the fact that at the former hospital there is a large autonomous gynecology service, whereas at the latter, gynecology is a subdivision of general surgery. This condition also obtains at the Beth Israel Hospital. Presumably, if the rate at the Peter Bent Brigham Hospital were corrected to exclude Jewish women and the figure given for hospital admissions were corrected to exclude patients admitted more than once, the rate of 148 per 100,000 would be increased.

Because studies of frequency of disease based on hospital statistics do not necessarily reflect the occurrence in the population at large, it was thought instructive to ascertain the prevalence and incidence of cancer of the cervix in a broader segment of the population. Statistics based on death certificates and clinic reports† show a prevalence of cervical cancer in the Commonwealth of 58.3 per 100,000 women in 1952 and an incidence for that year of 25.3 per 100,000 women (Table 5). The distribution of Jews and non-Jews in the Commonwealth of Massachusetts cannot be accurately determined.

Kennaway[1] discusses the role of strict observance of the Talmudic prohibition of sexual intercourse for seven days after the cessation of menses as a possible factor in prophylaxis of cervical cancer. In view of the fact that 15 of the 22 Jewish women with cancer of the cervix were Russian-born and that culturally the Russian Jew is less deracinated than almost any other immigrant group from the European diaspora, it seems unlikely that this factor is of significance. As in any group, strict observance of ritual prohibitions is largely a matter of individual conscience, and concupiscence frequently prevails over scriptural injunction. Although carcinoma of the penis is almost unheard of in circumcised Jewish men the relation of this ritual procedure to the infrequency of carcinoma of the cervix in Jewish women remains to be evaluated. Evidence indicates that the 22 Jewish women with cervical cancer reported on were married to Jewish men, who, presumably, were circumcised.

Of the 22 cases of cancer in Jewish women 3 merit special attention. In 2 cases invasive squamous carcinoma arose in the cervical stump after supracervical hysterectomy for multiple leiomyomas of the uterus. One of these was in a thirty-eight-year-old woman in whom a small exophytic, histologically proved papillary carcinoma developed two and a half years after supracervical hysterectomy; cervical biopsy had not been performed at the time of hysterectomy. Since implantation of radium she has remained well, and she is free from evidence of recurrent disease twenty-one years later. The other example of carcinoma of the cervical stump arose in a woman of sixty-four who had undergone supracervical hysterectomy, fifteen years previously, for multiple leiomyomas of the uterus and an endometrial polyp. There was extension of a squamous carcinoma of the cervix to the pelvic walls and metastatic tumor in aortic lymph nodes.

In spite of the rarity of carcinoma of the cervix in Jewish women supracervical hysterectomy is no more advisable in Jewish than in non-Jewish women. In this respect our experience coincides with that of Weiner et al.,[3] who found 6 cases of carcinoma of the cervical stump in Jewish women who had previously had supracervical hysterectomy. One of the cases of squamous carcinoma in situ with gland involvement occurred in a nulliparous, sixty-year-old Jewish woman; the diagnosis was made on microscopical examination of an asymptomatic cervical polyp found on routine physical examination. She has re-

TABLE 5. *Carcinoma of the Uterus, the Corpus and the Cervix in Jewish and Non-Jewish Women at the Beth Israel Hospital, Boston, and in the Commonwealth of Massachusetts.*

SOURCE	ENUMERATION	TOTAL UTERINE CARCINOMAS		INVASIVE CARCINOMA OF CORPUS		INVASIVE CARCINOMA OF CERVIX	
		NO.	RATE per 100,000	NO.	RATE per 100,000	NO.	RATE per 100,000
Beth Israel Hospital, 1928-1953 (histologically confirmed):							
Total women admitted	86,214	173	201	102	118	71	82.4
Jewish women	66,226	93	140	74	112	19	28.7
Non-Jewish women	19,988	80	400	28	140	52	260.0
Commonwealth of Massachusetts, 1952:							
Prevalence	2,461,327	1727	70.2	294	11.9	1433	58.3
Incidence	2,461,327	751	30.5	128	5.2	623	25.3

*Data kindly furnished by Dr. Herbert W. Horne, Jr.
†Data kindly furnished by Dr. Herbert L. Lombard.

mained free from recurrence for twelve years since complete hysterectomy. The chances that carcinoma in situ of the cervix will develop in a woman who is both nulliparous and Jewish are slight and make this case noteworthy.

Conclusions

Carcinoma of the cervix uteri occurs much less frequently in Jewish than in non-Jewish women. In the defined hospital population of this report the ratio was 1:9. By contrast, carcinoma of the corpus uteri occurs about as frequently in Jewish as in non-Jewish women. In the same population the ratio was 1:1.25. The data from which these ratios are derived were based exclusively on histopathologically confirmed cases of carcinoma of the cervix and corpus uteri.

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INFARCTION OF THE CARDIAC ATRIA*

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SEATTLE, WASHINGTON

THE diagnosis of acute infarction of the atrium of the heart is made very rarely in comparison with the probable frequency of its actual occurrence. This condition is seldom recognized during life. Atrial infarction occurred either as an isolated entity or as a concomitant finding with ventricular infarction in 17 per cent of the 182 cases of proved myocardial infarction reported in 1942 by Cushing et al.[1] Bean,[2] however, observed infarction of the atrium in only 3 of 300 autopsies involving myocardial infarction, and Wartman and Hellerstein[3] recorded a 7 per cent frequency among 132 infarcted hearts; isolated atrial lesions occurred in 4 of their 17 cases, and the remaining 13 showed combined atrial and ventricular involvement.

The purpose of this report is to present what is believed to be one of the first documented cases in which the diagnosis was established ante mortem on the basis of characteristic electrocardiographic alterations occurring during the course of an acute myocardial infarction, later confirmed at autopsy. Hellerstein,[4] in 1946, described a similar case.

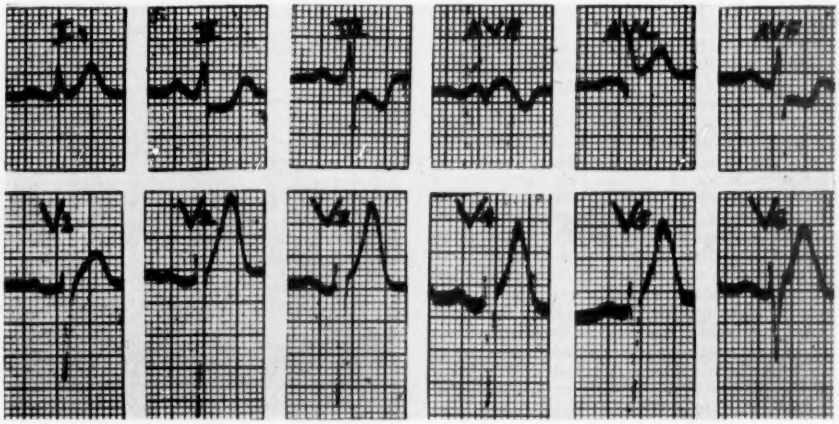

Figure 1. *Electrocardiogram Taken on the First Hospital Day, Showing Changes of an Acute Anterior Myocardial Infarction in a Heart with Striking Clockwise Rotation.*

Case Report

A 31-year-old police officer was admitted to the hospital because of intense and persistent precordial pain and shock-like state. One hour previously, while listening to a radio broadcast of an exciting football game, he had suddenly been seized with a severe, crushing retrosternal pain, which radiated across his chest in both directions and was accompanied by acute dyspnea and profuse perspiration. This pain continued without relief despite an injection of morphine, and was noted to radiate upward into both jaws and downward along both arms.

Physical examination revealed a large man who was obviously acutely ill, with striking pallor, labored respirations and cyanosis of the nail beds. There was no engorgement

*The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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of the cervical veins. Both lung fields were clear to auscultation except for a few scattered, crepitant, basal rales bilaterally. The heart was diffusely enlarged to percussion, and the sounds were weak and distant at a rate of approximately 160 per minute. The blood pressure was 100/80. No heart murmurs or valvular deformities were identified. The abdomen was roundly obese, without evidence of gaseous distention or hepatomegaly, and no abdominal or peripheral edema was present.

The diagnosis of acute myocardial infarction was made on clinical grounds, and appropriate treatment was instituted.

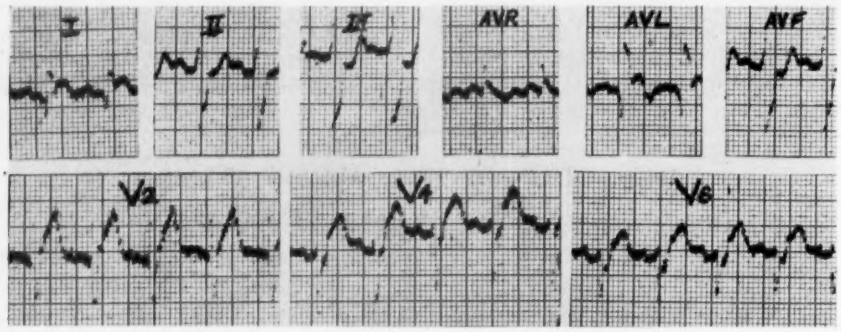

FIGURE 2. *Electrocardiogram Taken on the Fourth Hospital Day, Revealing an Acute Myocardial Infarction Involving the Anterior Wall, with Lateral and Septal Extension as well as Atrial Involvement (Note the PTa-Segment Deviations in All Leads).*

This included bed rest in an oxygen tent, with morphine as necessary for the intensely severe chest pain. Anticoagulant therapy with Dicumarol was initiated. During the 1st 2 days the patient's condition remained unchanged except for a gradual but continuous fall in blood pressure. Treatment during this 48-hour period included a liter of 5 per cent dextrose in water solution administered by hypodermoclysis because of dehydration resulting from repeated emesis, in addition to sedation, vasodilators, anticoagulants and morphine. An electrocardiogram taken on the day of admission (Fig. 1) showed acute myocardial infarction of the anterior wall, which, on serial tracings taken later, was seen to have both lateral and septal extensions as well as associated atrial involvement (Fig. 2 and 3). On the morning of the 3d day there was increasing evidence of cardiac decompensation, a persistent leukocytosis (count of 14,800), a temperature of 102°F., tachycardia (rate of 140) and persistent chest pain especially intensified by deep inspiration. The hypotension continued even after digitalization had been accomplished. Penicillin was given because of the elevated temperature and pulmonary congestion. On the 4th day the diagnosis of atrial infarction was made, and for 2 days dyspnea increased and Cheyne-Stokes respiration was evident at times. Rales indicative of acute pulmonary edema became pronounced throughout both lung fields. The respiratory rate became more rapid, and the patient began spitting up blood-tinged, frothy sputum. Pooling of blood in the extremities by means of inflated blood-pressure cuffs was attempted for several hours in preference to venesection, and this proved to be of definite although transient benefit. Mercurial diuretics were without effect. Despite phlebotomy and all other therapeutic measures he continued to fail, and died during the 7th hospital day.

At autopsy the pertinent findings were confined to the heart, which weighed 560 gm. There was hypertrophy of the walls of both the right and the left ventricle, with moderate dilatation of the right and left cardiac chambers. Approximately 150 cc. of fibrin-flecked fluid was present in the pericardial cavity. Deposits of fibrin were noted over the anterior and lateral surfaces of the left ventricle. On serial section the lumens of the coronary vessels demonstrated considerable narrowing owing to the presence of atherosclerotic plaques. At a point 1 cm. from the origin of the left coronary artery and extending into its anterior descending branch for a distance of 1.5 cm. was a thrombus firmly attached to the intimal lining of the vessel. The myocardium of the anterior and lateral walls of the left ventricle and anterior third of the septum was flabby in consistence and on section was mottled red and yellow. The anterior wall of the left atrium, including the appendage, showed similar changes; a mural thrombus was firmly attached to the endocardium on the anterolateral wall of the appendage. The valve leaflets were smooth and glistening. The endocardium lining the right side of the heart was not remarkable. There were congestion and edema of all abdominal viscera.

Microscopical sections taken from the anterior wall of the left atrium (Fig. 4 and 5) disclosed fragmentation of the muscle fibers, with loss of striations. The nuclei were in various stages of degeneration. Edema fluid between the muscle fibers contained collections of leukocytes (predominantly polymorphonuclear cells) and a large number of red blood cells. Similar changes were seen in sections from the septum, as well as the anterior and lateral walls of the left ventricle. The thrombi were of recent origin, with no evidence of organization.

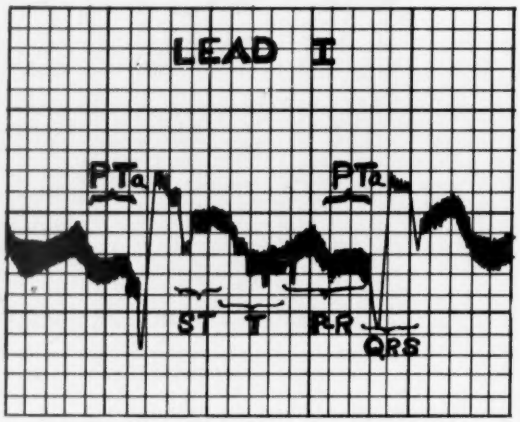

FIGURE 3. *Enlargement of Lead 1 from Figure 2, Showing the PTa-Segment Deviations.*

DISCUSSION

Because of the various complications that often follow or accompany infarction of the cardiac atrium this diagnosis should be kept in mind, and the condition promptly recognized when it does occur. The most frequent complications associated with or precipitated

by atrial infarction are the various atrial dysrhythmias.[5-8] Mural thrombi, with resultant embolic phenomena, and aneurysmal dilatation of the atrial wall, with subsequent rupture, are far less common sequelae than the disorders of atrial rhythm.

The changes in the electrocardiogram most suggestive of atrial infarction are an elevation or depression of the PR segment (corresponding to similar deviations seen in the ST segment with ventricular infarction) and the sudden development of atrial dysrhythmias. The terminal portion of the PR segment that is representative of the period of atrial repolarization is commonly referred to as the atrial T wave and has been termed, by Abramson et al.,[7] the PTa segment. The direction of displacement from the isoelectric line of this segment is dependent, theoretically, on the location of the infarcted area within the atrium, just as the deviation of the ST segment in ventricular involvement is governed by the anterior or posterior site of infarction.[6,7] An elevated PTa segment in the electrocardiographic leads reflecting the potentials of the posterior aspect of the heart (Leads 2, 3 and aVF) would be indicative of posterior involvement. Conversely, an infarction of the anterior wall would give rise to PTa-segment elevation of Leads 1 and aVL and the anterior precordial or V leads overlying the injured area, and a coexistent, reciprocal depression of the PTa segment in Leads 2, 3 and aVF might also be seen. In some cases with circumferential involvement of the appendage various combinations of PTa-segment deviations are to be expected.

FIGURE 4. *Photograph of a Cross-Sectional Specimen from the Atrium, Showing the Region of Infarction and Illustrating the Origin of Figure 5 (Prepared by the Armed Forces Institute of Pathology).*

Despite an accurate clinical diagnosis in the case presented above, the magnitude of the myocardial destruction and the extent of coronary-vessel involvement, as shown at autopsy, made it impossible to prevent the patient's death. In cases of lesser severity it is conceivable that the recognition and treatment of an atrial infarct at the time of its occurrence could, by preventing serious complications, be life saving.

FIGURE 5. *Photomicrograph, Showing an Enlarged View of the Site of the Atrial Infarction (Prepared by the Armed Forces Institute of Pathology).*

SUMMARY

The clinical and electrocardiographic findings together with the autopsy data are presented in a case of acute myocardial infarction with both ventricular and atrial involvement. The diagnosis, made ante mortem on the basis of electrocardiographic changes, was confirmed at autopsy. The importance of promptly recognizing this condition is discussed, and the changes in the electrocardiogram occurring with atrial infarction are reviewed.

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MEDICAL PROGRESS

CANCER OF THE GENITOURINARY TRACT (Concluded)

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BOSTON

Treatment

The various therapeutic measures comprise cystoscopic fulguration or resection with the McCarthy resectoscope, transurethral implantation of radioactive materials such as radon seeds, the use of liquid radioactive isotopes within a distensible bag catheter, suprapubic electrodesiccation and resection with or without the implantation of radioactive materials, segmental resection of lesions confined to the distensible portions of the bladder, with or without division and reimplantation of a ureter, unusual operations such as radical prostatectomy combined with excision of the tumor-bearing area at the bladder neck, simple cystectomy, radical cystectomy with lymph-node dissection, pelvic evisceration, deep radiation therapy and combinations. The varied location, extent and character of tumors make all these technics of value at times.

There is fairly general agreement at present regarding the treatment of papillomas and superficial papillary cancers situated in or near the bladder base. The use of the resectoscope for coagulating and resecting such tumors is almost standard procedure. Small papillomas situated on the anterior wall or upper lateral walls and vertex are often excised satisfactorily in this way, but larger tumors located in these areas are probably more effectively treated by a suprapubic operation, with coagulation and resection of the tumor down to the normal-appearing bladder muscle or segmental removal of the tumor and underlying bladder wall. Larger and more deeply infiltrating tumors of the bladder base may be treated by the resectoscope, care being taken to resect deeply into the bladder muscle. Milner[41,42] has written most extensively on this phase of therapy, and his results have been encouraging. Radon seeds may be implanted through the cystoscope in the base and about the margins of tumors that are found on pathological examination to have infiltrated the bladder muscle. This is an additional safeguard.

Other urologists, who prefer suprapubic cystotomy and treatment of such tumors under direct observation, use the electrosurgical method of desiccation with a disk electrode and resection of the desiccated tissue with a loop. Radon seeds, radium itself or some other radioactive element may be implanted in the base and about the margin of the tumor. When the tumor is located away from the trigone it is probably better to carry out segmental resection, after desiccation of the lesion to prevent implantation of viable cells in the wound.

The treatment of superficial multiple papillary tumors by the introduction of radioactive material in the center of the balloon of a specially designed Foley catheter, as suggested by Schulte et al.[43] in this country, occasionally seems useful though projecting tumor should probably be resected completely beforehand. Another method is the use of radioactive solutions in a balloon catheter, as advocated by Walton and Sinclair[44] in England. In the presence of multiple, rapidly recurring tumors of this sort cystectomy has been most worth while.

Larger and definitely infiltrating papillary cancers require wide segmental resection when located so that partial removal of the bladder is possible, with or without division and reimplantation of a ureter as necessary. Large, deeply infiltrating tumors occupying the bladder base require total cystectomy and diversion of the urine to the bowel or the skin.

Primary, infiltrating epidermoid or squamous-cell cancers, no matter how small, are difficult therapeutic problems and are seldom controlled. One reason is the difficulty in determining with certainty the cellular limits of the tumor. This usually results in underestimation of extent and inadequate primary therapy. It is a question whether such cancer should ever be treated by transurethral methods although theoretically and actually some small lesions in the bladder base can be and have been treated by resection and local implantation of radon seeds. It is probably best to carry out a wide segmental resection of tumor in the distensible portion of the bladder and to do radical cystectomy and pelvic-lymph-node dissection for lesions involving the bladder base. My experience indicates that, if metastasis to pelvic lymph nodes has occurred, radical cystectomy is probably of only palliative value. Whitmore and Marshall,[45] who have had most experience with radical pelvic surgery for cancer of the bladder, have tried radical cystectomy and total pelvic evisceration in a reasonably large number of cases, with a significantly better control rate. It does seem, in spite of generally poor results from surgery, since epidermoid cancer of the bladder is not controlled by deep x-ray therapy, that radical cystectomy offers the only hope and should be done as early as possible. One likely reason for the present poor results is that less radical treatment is often first attempted and radical cystectomy only carried out if previous treatment fails. My inclination at present is to recommend and to do radical cys-

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tectomy if there is no evidence of distant metastases or extensive local involvement of the pelvic lymph nodes and if no fixation by local extension is demonstrated. Radical cystectomy is of little avail unless these criteria are adhered to and, when attempted for more extensive disease, will simply lead to failure. Pelvic evisceration is probably worth while for tumors of the bladder base extending deeply into the bladder wall or through the bladder wall about the seminal vesicles; in such cases involvement of the anterior wall of the rectum is quite likely.

Cystectomy has yielded good results when performed for transitional-cell tumors (multiple papillomas or papillary cancers) but generally poor results when applied to the treatment of epidermoid cancers. For this reason and because of the magnitude of surgery involved in cystectomy and diversion of the urinary stream necessitated by cystectomy the indication for this procedure in the minds of most urologists is still not clear. It seems certain, however, that there is no really good alternative to radical cystectomy since palliative procedures are at least equally unsatisfactory and deep x-ray therapy, except in an occasional case, has not been helpful. It may be that, for lesions too extensive for possible cure by cystectomy, diversion of the urine to relieve bladder symptoms and protect renal function is the best that can be done. Foley and his associates[46] have advocated deep electrodesiccation of such tumors after vena-cava ligation to prevent pulmonary emboli but no data regarding its efficacy are available.

Much discussion has recently revolved around the best method of diversion of the urine. The procedures available are cutaneous ureterostomy, nephrostomy, ureteroenterostomy and the construction of an artificial bladder by implantation of the ureters into an isolated pouch of cecum (Merricks et al.[47]) or ileum (Bricker[48]). Couvelaire[49] has recently attempted to solve this problem by doing ureterointestinal anastomosis into an isolated loop of ileum, which is anastomosed to the stump of the membranous urethra.

Certainly, the patient is most comfortable when division is accomplished by ureteroenterostomy, but operative mortality and the long-term results have been so poor in terms of complications from hyperchloremic acidosis, hydronephrosis and pyelonephritis, leading to disability and death from sepsis or uremia (Colby[50]), that many urologists doubt the advisability of ureteroenterostomy. Cutaneous ureterostomy has been adopted by Marshall as a more satisfactory procedure in his hands, and other clinics have been exploring the results of implantation of the ureters into a cecal pouch or ileal loop. The ileal loop is being tried at present because the urine drains promptly from the bowel, obviating absorption of electrolytes, which is one of the main difficulties encountered after conventional ureterointestinal anastomosis. This procedure, however, does not guarantee the integrity of the upper urinary tract unless the anastomoses between the ureters and the bowel can be performed without resulting stricture. Early results are encouraging, but longer periods of observation must be awaited before the ultimate result can be evaluated.

Cutaneous ureterostomy, even though simple, is full of complications and the necessity for scrupulous care of tubes, which unfortunately come out, block and cause stricture of the ureter that makes their reintroduction difficult or impossible. Nephrotomy has many of the same disadvantages. All patients with an ileal loop require a urine-collecting apparatus, which may not always work well.

A complete discussion of this subject is impossible here, but it does seem that for many reasons ureteroenterostomy is still the best procedure. It has become obvious that hyperchloremic acidosis of a troublesome degree is usually a reflection of impaired renal function resulting from pyelonephritis or hydronephrosis or both, making the reabsorption of electrolytes (ammonia and chlorides) from the bowel that contains urine a burden that renal function is unable to cope with successfully (Rosenberg,[51] Lapides[52] and Mitchell and Valk[53]); the crux of the problem is therefore whether the operation can be done in such a way that obstruction at the site of anastomosis, with resultant hydronephrosis and pyelonephritis and impaired renal function, can generally be avoided. It has become obvious that the Coffey I type of operation, with its submuscular implantation, provides in fact a valve that prevents reflux of bowel contents into the ureter but that stricture of the segment of ureter left projecting into the bowel lumen often occurs because of intense inflammation. This difficulty probably accounts for many poor results. The Nesbit[54] direct elliptical anastomosis was developed to solve this problem, which it generally did, but unfortunately gave such a wide stoma between bowel and ureter that gas and even fecal matter refluxed into the upper urinary tract, with consequent severe pyelonephritis and rapid deterioration of kidney function. This procedure has therefore been generally abandoned except for anastomosis between ureter and free-draining ileal loop. Cordonnier[55] described and utilized an end-to-side anastomosis of the ureter and bowel with which he has obtained good results. The absence of a tunnel seems to make reflux a distinct possibility.

A modification of the Coffey and Nesbit procedures that combines the submuscular tunnel of Coffey with direct anastomosis between the terminal cut end of ureter and the mucosa of the bowel has been described.[56] This has become known as the "combined" technic. In experimental work in animals (Woodruff et al.[57] and Weyrauch and Young[58]) this operation gave the best results of all methods tried, and in clinical application it has been successful in a large number of cases. An experience of five years indicates that the initially good results have per-

sisted so that, since the postoperative condition of the patients is much more normal and satisfactory than that of patients with cutaneous ureterostomy or artificial bladders of any sort, ureteroenterostomy is still being performed at the New England Medical Center and is considered the procedure of choice. Long-term results may indicate that the valve created decompensates so that hydronephrosis and pyelonephritis may ultimately develop in many cases; at present, however, and until patients die of renal disease instead of recurrent cancer, ureteroenterostomy can probably be considered the best method of diverting the urine except in patients with low renal reserve from any type of nephritis or when dilatation of the upper urinary tract is so severe that ureteroenterostomy is technically impossible or unsafe.

It is the contention of the New England Medical Center that postoperative death from ureteroenterostomy should rarely occur. The mortality due directly to complications of ureteroenterostomy at the Center has been 1 in 40 patients. Cases of clinical pyelonephritis and troublesome hyperchloremic acidosis have been few. One must be prepared, however, in the event that stricture of significant degree develops at the site of anastomosis, to reimplant the ureter in the bowel or carry out cutaneous ureterostomy or nephrostomy promptly to conserve kidney function. In the event of failure one could implant the ureters into an ileal loop or into an isolated pouch of cecum. It can be stated that no patient who has survived cystectomy and ureteroenterostomy should die within a reasonable period from renal disease because either re-exploration of the ureter or external drainage should be done as soon as it is obvious that ureterointestinal anastomosis has failed. The patient is then no worse off than he would have been with external urinary drainage in the first place.

Two other methods of performing ureteroenterostomy have been described — one by Mathisen[59] and the other by Goodwin et al.[60] The Goodwin technic is the same as that described above except that anastomosis is carried out through the open bowel (colotomy), which seems to have little advantage and the distinct disadvantage of introducing another possible source of leakage from the bowel. The Mathisen operation, which is in essence the construction of an intraluminal papilla of terminal ureter wrapped in a preformed, full-thickness, longitudinal section of bowel wall, has not, in my hands, been satisfactory in animals though more technical experience may change this opinion.

The subject of ureteroenterostomy must not be dismissed without the statement that, for repeatedly good results, the operation must be done with great care, and considerable experience or expert guidance is necessary to avoid immediate complications.

The final recommendations for the treatment of infiltrating cancer of the bladder are wide segmental resection when possible, radical cystectomy in the absence of obvious distant metastases or extensive local or widespread pelvic-lymph-node metastases and, occasionally, pelvic evisceration when the condition, age of patient and local disease seem to offer a chance for cure. It is admitted that the results will be poor, but they can only at present be improved by aggressive surgical attack. The goal should be to cut down operative time, decrease complications and speed convalescence so that if cure is not obtained at least worth-while palliation will result. The occasional cystectomist and ureteroenterostomist will not succeed in achieving this end.

The diagnosis and treatment of sarcoma of the bladder and adenocarcinoma need no special comment since biopsy usually makes the diagnosis and treatment as dictated by the location, extent of the disease and condition of the patient follow the same principle as that used for infiltrating epidermoid cancer.

Cancer of the Prostate

The statistics on the frequency of prostatic cancer are so well known as to need no comment here.

Early Cancer

Evidence is accumulating that the radical operation is of value for cancer confined to the prostate. Jewett[61] found that, of 132 patients on whom radical perineal prostatectomy was done before May, 1943, at the Brady Urological Clinic at the Johns Hopkins Hospital, 52 (32 per cent) lived or were living five years or more without evidence of recurrence of metastases. Of 63 patients who lived or were living ten years after operation 12, or 19 per cent, were without evidence of cancer. Of the 132 patients there were 78 in whom microscopical extension of cancer outside the prostate had not occurred. Of these, 40 (51.3 per cent) lived or were living five or more years without evidence of cancer; 43 of the 78 patients had been operated on ten or more years before and 12 lived or were living for ten to twenty-seven years without demonstrable cancer — a ten-year survival of 28 per cent. Colby,[62] in a study of radical operations for cancer of the prostate performed at the Massachusetts General Hospital, reported that 51.7 per cent of 29 patients who had had radical prostatectomy five or more years before were alive and clinically free of disease.

In an effort to compare these survival figures with results obtained by palliative treatment of similar lesions Barnes[63] studied 31 patients with early prostatic cancer. He found that 16, or 53 per cent, lived five years or longer and 7, or 22 per cent, ten years or longer, indicating no great advantage, so far as survival is concerned, for radical surgery as contrasted with palliative therapy. It must be pointed out, however, that even if these figures are considered representative of the usual course of events after the diagnosis of early cancer of the prostate and the adoption of palliative therapy, no patients

are cured. On the other hand it must be considered that the patients who survived for ten years after radical prostatectomy without evidence of residual disease or metastases were cured. When recurrence or metastasis takes place after radical prostatectomy palliative therapy is probably just as effective as it would have been if given in the presence of the primary disease.

These studies have served to stimulate more interest in the radical operation for early cancer of the prostate, and it is obvious from the many reports in the literature that urologists have generally accepted the value of early diagnosis and radical operation. This point of view has been strengthened to some extent by the introduction of radical retropubic prostatectomy, first by Millin et al.[64] in England and later by Memmelaar[65] in this country; more recently Chute[66] and Lattimer et al.[67] have advocated this procedure, which now allows surgeons unfamiliar with the perineal operation opportunity to do radical prostatectomy. The radical operation performed by the perineal route has often been considered a difficult one associated with many complications owing to rectal injury or incontinence. My own experience, based on about 100 radical prostatectomies and 7 radical retropubic prostatectomies, indicates that the operation is no easier when performed through the abdomen and is, if anything, less satisfactory because of the difficulty of performing anastomosis between the bladder and membranous urethra. It has a disadvantage in that biopsy of the gland is not possible until the membranous urethra is transected and the prostate mobilized upward. One is therefore theoretically committed to the operation from the start. It would be possible, however, to free the gland, biopsy it and replace the prostate, without anastomosing the urethra, by means of a urethral splinting catheter if cancer was not found, though I have not heard of cases in which this technic was carried out. An advantage of the operation is the opportunity to explore the abdomen and retroperitoneal area for visceral or lymph-node metastases that is denied the perineal prostatectomist, though such information would simply obviate the desirability of radical surgery and positive findings would be very unusual in properly chosen cases. My own observation is that the incidence of postoperative stricture of the urethra and incontinence must be about the same regardless of the type of operation. These complications have generally been due to improper surgical technic, injury to the triangular ligament by dissection or retraction or improper placing of anastomosing sutures between the bladder neck and the urethra. Mortality is a minor consideration since only 1 death has occurred in my series.

On the basis of experience in radical surgery for early cancer of the prostate it has become increasingly important to make the diagnosis early while the disease is confined to the gland. This can at the present time be accomplished only by palpation of a suspicious nodule in the prostate in the course of routine examination because there are no symptoms of early carcinoma of the prostate per se. Patients seen by the urologist with urinary complaints usually present themselves because of some other condition such as associated benign hyperplasia or infection. This puts the burden on general practitioners who, collectively, each day examine many men in the older age group. Any area of induration that fails to disappear or soften on massage must be considered suspicious of cancer. Calculi may be ruled out by plain x-ray films of the prostatic area. Diagnosis depends on biopsy, either by needle through the perineum or by open incision of the perineum. Removal of tissue by transurethral resection is rarely helpful in early cases because of the location of the malignant lesion in the periphery of the gland. Papanicolaou stain of prostatic secretion does not appear to be of great help in the diagnosis of early cancer but may be tried. Before radical surgery is decided on for early cancer of the prostate, x-ray study for bone metastases is necessary, as is estimation of the acid phosphatase; this will prevent ill chosen radical surgery in an occasional case. Estimation of acid phosphatase done in the conventional way will not reveal elevation when disease is confined to the gland. Recently, Fishman et al.[68] devised a test for determination of prostatic acid phosphatase based on the inhibitory action of L-tartrate on prostatic acid phosphatase that is almost specific and has demonstrated elevation of the prostatic portion of total serum acid phosphatase when the total acid phosphatase is either not elevated or only slightly elevated. This test may therefore be of great value in the study of early as well as of late cases of cancer of the prostate and will probably come into general use. In a patient with a suspicious or proved lesion and no metastases who is in general good health and has a good life expectancy, radical prostatectomy is indicated. If the perineal operation is chosen biopsy can be made; if the biopsy is positive the radical operation is carried out. Unfortunately, at the present time only about 10 per cent of patients with cancer of the prostate fall into this classification, and, therefore, one must concentrate on earlier diagnosis.

Extensive Local Carcinoma

Four methods of treatment are applicable to local disease that has probably extended beyond the confines of the prostate or has metastasized.

The work of Huggins, which demonstrated the androgen dependence of most prostatic cancers, led to bilateral orchiectomy or the administration of stilbestrol or a combination of both as a means of providing palliative therapy for extensive prostatic cancer. This has become standard palliative therapy, and its results were analyzed by Nesbit and Baum[69] in 1950 in a study of 1818 cases pooled

from the collective cases of a group of physicians representing a cross section of standard urologic practice in North America. This study clearly demonstrated the advantage of combining orchiectomy and subsequent stilbestrol administration. Thus, of 324 patients without metastases when first seen, 44 per cent survived for five years when combined therapy was given whereas when either stilbestrol or orchiectomy was used independently only 30 per cent survived. The report also demonstrated the gravity of metastatic disease since in 260 patients who had metastases when first seen combined therapy led to only a 20 per cent five-year survival.

At present many urologists rely exclusively on this type of palliative management, but attempts have been made to do better as evidenced by three other types of therapy described. Several urologists have tried the following plan of therapy: patients with early, palpable extension of disease about the seminal vesicles but without evidence of distant metastases have been first treated with stilbestrol; after tumor regression has occurred radical prostatectomy has been done. A recent report by Scott,[70] of Rochester, New York, on 21 patients so treated after thirty-six or more months, states that the average interval after endocrine therapy was first instituted was sixty-five and three-tenths months; the average time after radical prostatectomy was forty-nine and eight-tenths months. The thirty-six-month survival rate was 85.7 per cent, which compared very favorably with that of 66 per cent after castration and stilbestrol therapy reported by Nesbit and Baum.[69] Scott[70] believes that the results warrant further trial. William Wallace Scott, editor of the *Year Book of Urology*, in a footnote to Scott's article of the 1953-54 year book, states that "conversation with Dr. Hugh Jewett revealed that there had been no five-year survivals among patients so treated at the Brady Urological Institute of the Johns Hopkins Hospital." This phase of the subject obviously deserves further investigation. It might be well, if such cases are to be treated as thoroughly as possible, to carry out orchiectomy at the same time. Hudson[71] is following this procedure in all radical prostatectomies.

Flocks and his co-workers[72] have attacked this problem in another way. For patients with extensive local disease but without demonstrable metastases they have, through the open bladder, injected radioactive gold into and about the prostate. At the time of their report of 129 patients so treated, the size of the palpable neoplasm had rapidly decreased in 98 per cent. Complications had been almost exclusively confined to rectal irritation, of which 15 patients in the first 50 and 3 in the subsequent 67 complained. Four had rectal ulcers, 3 of whom required colostomy. Of the 50 patients followed 27 were alive and 7 had died without clinical evidence of disease, 8 were alive with disease and 8 had died of disease. Stilbestrol had been given to 24, and 1 had had orchiectomy. A recent communication from Flocks[73] states that as of January 1, 1954, about 270 cases had been so treated; 100 cases had been followed for eighteen to twenty-four months. Of these 100 patients 30 had involvement of pelvic lymph nodes. Only 1 of the 30 remains alive and well without definite evidence of tumor, though others are living with obvious tumor remaining. Of the other 70 without evidence of pelvic-lymph-node involvement at the time of treatment 32 are alive, with no evidence of tumor. The remaining 38 have evidence of cancer or have died. Approximately 20 per cent of the 100 patients have died during the period of observation. Dr. Flocks adds that "we are continuing to be enthusiastic with regard to this technique." Much more time must elapse before the results of this type of treatment can be evaluated and compared with those of other methods.

Another possibility in extensive local disease is radical prostatovesiculocystectomy with ureteroenterostomy, which has been carried out occasionally by a number of surgeons. In my hands this has been done for a few patients with local disease that has either failed to respond to orchiectomy and stilbestrol or relapsed after palliative therapy. Most patients have shown local disease involving the external sphincter or the bladder base, with developing obstruction of one or both ureters. Cases must be chosen carefully, but a few brilliant results have been obtained.

Treatment of Relapse after Palliative Orchiectomy or Stilbestrol

Again Huggins has led the way in an effort to provide further palliation by eliminating or suppressing remaining androgen production in the adrenal glands of patients with reactivated prostatic cancer after a period of control by orchiectomy or stilbestrol therapy or both. Four other methods of treatment have been tried — bilateral total adrenalectomy, hypophysectomy, shunting of adrenal blood through the portal circulation so that androgen produced by the adrenal gland will be destroyed or inactivated in the liver, and the use of cortisone, which may act by suppressing pituitary ACTH production and thus indirectly result in diminished production of adrenal androgen.

Bilateral adrenalectomy. Bilateral adrenalectomy was first performed by Huggins and Scott[74] before cortisone was available and was later reported by Huggins and Bergenstal,[8] with a favorable response in few cases. Since then many surgeons (including Leadbetter,[75] Harrison,[76] Baker,[77] Whitmore[78] and Scardino and Prince[79]) have reported results obtained in small series of patients. In general results have

been disappointing because only short periods of relief from pain have been obtained, but a few long-term good results have been reported. The consensus, after several years' trial, is that one cannot predict with certainty the result to be expected in a given case and that the operation usually results in little change in the course of the disease. I believe that there is little justification for bilateral adrenalectomy for this purpose and that it will be done only rarely unless criteria can be established that allow better choice of cases. Theoretically, the type of case that one might expect to respond is disease that has responded to orchiectomy and stilbestrol and can be shown to be still under endocrine control. This may be accomplished by testosterone administration, which results in increased pain or rise in serum acid phosphatase. An indirect method is to give cortisone, which probably indirectly suppresses androgen production through its effect on the pituitary gland and thus relieves pain in androgen-sensitive cases.

Hypophysectomy. Scott[80] has studied the effect of hypophysectomy on a few patients with extensive prostatic cancer and has demonstrated its value in a limited way. This operation is not likely to become widely used for two reasons: complete hypophysectomy is rarely possible and a palliative procedure of this magnitude is not easily entered into. It may provide a useful investigative method.

Shunting operation. The demonstration that the liver is a physiologic filter for testosterone propionate, by Grayhack and Scott,[81] suggested to the group at the Brady Clinic of the Johns Hopkins Hospital an operative procedure to allow shunting of venous blood from the left adrenal gland through the portal circulation. This operation divides all the arterial and venous channels carrying blood to and from the left adrenal gland except for the adrenal artery arising from and the vein entering the left renal vein. The spleen is then removed, and anastomosis performed between the left renal vein and the splenic vein. After recovery from this and demonstration of good function of the left kidney, the right adrenal gland is removed. Scott stated in a recent talk before the New England Section of the American Urological Association that 3 patients had been operated on in this manner and that the palliative effect had been good. This ingenious method may be of value, and follow-up results should be most interesting. This seems likely to present a further investigative method.

Cortisone administration. Another approach to the problem is an attempt to suppress the formation of adrenal androgens by cortisone administration. Huggins and Bergenstal[8] made the statement that aside from producing a euphoric state cortisone had little effect on prostatic cancer in relapse. There are, however, experimental and clinical indications that the hormone does in fact probably suppress the formation of pituitary ACTH and that when relapsing carcinoma of the prostate is still susceptible to androgen stimulation or withdrawal cortisone results in indirect suppression of androgen formation in the adrenal glands, with consequent improvement in terms of relief of pain and sometimes decrease in serum acid phosphatase. It has not yet been shown that the course of the disease is significantly changed. This subject, which was introduced by Leadbetter, Ganem and Solomon,[75] has more recently been discussed by Hayward[82] and Valk and Owens,[83] who gave extended consideration to the hormonal interrelations of pituitary gland, testes and adrenal glands. It appears that the effect of cortisone may be the suppression of formation of luteinizing hormone in the pituitary gland that normally stimulates both the Leydig cells of the testes and the cells of the reticular zone of the adrenal cortex to produce androgen. It is assumed that after orchiectomy the adrenal cortex is responsive to luteinizing hormone; furthermore, it seems likely that the response to estrogen therapy may be due to suppression of follicle-stimulating hormone. Estrogen, however, may stimulate the formation of luteinizing hormone, with ultimate increased androgen secretion and reactivation of prostatic carcinoma. It seems, therefore, that since there is evidence that cortisone suppresses the formation of luteinizing hormone (Wilkins and his group have shown that as little as 25 mg. a day will suppress excessive androgen formation in cases of adrenocortical hyperplasia, and others have stated that atrophy of the adrenal cortex may occur after prolonged or excessive cortisone administration, with adrenal insufficiency and death), the use of the drug to produce a medical suppression of adrenal function for further control of androgen-sensitive prostatic cancer is quite reasonable. My experience is now based on its successful use in more than 10 cases of relapsing cancer of the prostate with extensive metastases after periods of control by orchiectomy and stilbestrol. Several patients have lived for more than a year after cortisone administration was begun. Valk and Owen reported its use in 8 patients, with good response in 6. Haywood reported 1 case and called attention to 3 others with favorable response. Results have in general been better than those after bilateral adrenalectomy. Several patients have not responded and presumably have androgen-independent cancer. Some undesirable effects have been observed: edema from sodium retention in spite of a low-salt diet and depletion of potassium, requiring supplementary medication. Since gastric hydrochloric acid secretion is increased cortisone must be given carefully to patients with an ulcer history. Dosage has in my experience been arrived at by administration of as much cortisone as is necessary to produce a clinical response, 100 to 200 mg. a day, followed by gradual reduction of the dose until symptoms reappear. Several patients have required less than 25 mg., others 25 mg., and still others between 25 and 100 mg. a day to be comfortable.

At present an outline for the treatment of cancer

of the prostate seems to be somewhat as follows: early cancer confined to the gland is treated by radical perineal or retropubic prostatectomy; local cancer with extension about the vesicles and without demonstrable metastases is managed by orchiectomy or stilbestrol, or both, to produce local regression, after which radical prostatectomy may be tried; orchiectomy and stilbestrol for palliating this type of case, or injection of radioactive gold may be used; cancer with metastases regardless of the local situation is treated with orchiectomy and stilbestrol as primary therapy; and in reactivated disease, if no metastases are demonstrated and the patient's condition warrants it, radical prostatovesiculocystectomy and ureteroenterostomy occasionally seem warranted. My preference for further palliative therapy at present is the use of cortisone. In some cases, for pain that is well localized, deep x-ray therapy may be of value. Further experimental and clinical investigation may alter these opinions. A last observation is that occasionally reactivated cancer of the prostate or even primary cancer of the prostate responds to the administration of androgens rather than estrogens.

Fibrinolysin Associated with Prostatic Cancer

One must not leave the subject of cancer of the prostate without calling attention to the work of Tagnon and Whitmore[84] demonstrating fibrinolysin in the serum of a small group of patients with disseminated prostatic cancer that may have been responsible for purpuric manifestations and bleeding from the gastrointestinal or urinary tract. These writers have provided evidence that the cancer tissue produces the fibrinolytic enzyme. At the New England Medical Center 6 patients with this bleeding tendency have been studied carefully by Stefanini.[85,86] Two cases in which bleeding was so severe that the patients' lives were in danger were reported. The bleeding tendency could not be controlled by transfusions or estrogen administration. It was discovered that cortisone quickly controlled the bleeding tendency and, in 1 case, allowed orchiectomy to be done, to establish endocrine control of the neoplasm. Stefanini believes that the effect of ACTH or cortisone is to increase the antifibrinolytic activity of the plasma and perhaps decrease the amount of available profibrinolysins. Other explanations are possible, and more work must be done before specific information can be obtained. It must be pointed out, however, that the bleeding tendency in a man with prostatic cancer is a serious manifestation that warrants study for fibrinolytic activity in the serum. If it is found, cortisone, in a dosage of 100 to 200 mg. daily, will prove effective in combating the effect of the production of this enzyme and may be life saving.

Tumors of the Testis

Tumors of the testis, an exceedingly interesting group of lesions, ordinarily metastasize by way of retroperitoneal lymphatics to the retroperitoneal lymph nodes, which usually are primarily located in relation to the origins of the spermatic blood vessels on the left side the level of the renal pedicle and on the right to lymph nodes about the cava some distance below the renal pedicle. The exception to this is chorionepithelioma, which spreads largely by blood-vessel invasion. It should be pointed out that pelvic and inguinal glands are rarely primarily involved unless the tumor of the testes involves the epididymis or the scrotal tissue. Blood-borne metastases occur and must be searched for. These observations form the basis for evaluation and treatment of the tumor.

All testicular masses that are not clearly the result of trauma or inflammation should be considered tumor until proved otherwise. Exploration, after occlusion of the spermatic cord, always makes diagnosis possible. Metastases to the retroperitoneal lymph nodes is often demonstrated by intravenous urography, which discloses displacement of a ureter about an enlarged node. Palpation of the supraclavicular areas, x-ray study of the chest and urine assay for chorionic gonadotrophic hormone may be helpful. In the past orchiectomy followed by deep x-ray therapy to the retroperitoneal areas, supraclavicular areas and mediastinum has been the method of treatment except in the hands of a few urologists, who have performed radical dissection of the retroperitoneal nodes.

The evaluation of these tumors has been brought under sharp scrutiny since the War largely by the report of Friedman and Moore,[87] in 1946, of 922 tumors of the testis observed among the 11,000,000 in the armed forces — a frequency of about 1 in 10,000. Their classification of testicular tumors has done much to clarify the confused pathological grouping formerly utilized. They found that by simple criteria almost all tumors fell into 6 groups: seminoma, 35 per cent; teratocarcinoma, 35 per cent; embryonal carcinoma, 19 per cent; teratoma, 7 per cent; miscellaneous tumors, including chorionepitheliomas, 3 per cent; and interstitial-cell tumors, 1 per cent. In 1948 Lewis[88] reported 250 cases treated at the Walter Reed Hospital in Washington, pointing out the value of retroperitoneal-lymph-node dissection, which had largely fallen into disuse. Again, in 1953, Lewis[89] described the results of treatment of 133 patients with radioresistant tumors followed for five years. His experience is so much larger than that of any other urologist that it seems best to consider his operative results as a base line from which treatment and results may be gauged.

It is important to note that seminoma is the only certain radiosensitive tumor of the testis. Complete destruction of the tumor is accomplished by less than 3000 r. My experience indicates that about 2000 r is effective. This is supported by Lewis's[89] report of 115 seminomas with only a 7 per cent mortality from metastases, though 4 additional patients died from the effect of unnecessarily high radiation doses. Five-

year survival was 89 per cent. Patients who died from metastases had very numerous or very extensive metastases. This suggests that one should expect about a 90 per cent survival from orchiectomy and deep irradiation therapy in this group of tumors. This has actually been my experience in a much smaller series of cases. Lewis does not advise retroperitoneal-lymph-node dissection, therefore, for seminoma. Kimbrough and Cook,[90] however, on the basis of Friedman's observation that of 319 patients with seminoma 11 had metastases showing embryonal carcinoma, teratocarcinoma or some other type, have stated that radiation therapy alone cannot be depended on to control metastases from seminoma and recommend retroperitoneal-lymph-node dissection as well as radiation therapy for seminoma. It seems possible that Friedman's observation did not necessarily imply that seminoma cells gave rise to other types of cells but rather that the primary tumor was not sectioned and studied carefully enough to show areas of embryonal carcinoma or teratocarcinoma from which radioresistant metastatic tumor developed. This simply serves to emphasize the point that all tumors must be serially cut and many blocks sectioned and studied instead of radical dissection of the retroperitoneal lymph nodes in all cases of seminoma. Lewis points out that all tumors other than seminomas usually require a tumor dose of more than 3000 r for effective therapy and some, particularly teratocarcinoma, radiation in excess of 5000 r. My observation is that some embryonal carcinomas are controlled by less than 3000 r, but one cannot tell with certainty which tumors will respond. Therefore, it seems best to carry out radical retroperitoneal-lymph-node dissection on the same side as the testis involved for all tumors other than seminoma and chorionepithelioma. This should be done to establish the presence or absence of involvement and to remove metastatic lymph nodes. Chorionepithelioma, which metastasizes largely by vascular channels, is treated by orchiectomy alone.

Lewis's five-year results of treatment of 133 radioresistant tumors of the testis indicated that only 1 of the patients with apparently inoperable metastatic disease treated by orchiectomy and radiation therapy was alive five years later. This patient had teratocarcinoma and a solitary skull metastasis, which was removed surgically. Thirty-eight, or 67 per cent, of 55 patients in whom dissection of the retroperitoneal lymph nodes was negative for metastases and in whom deep x-ray therapy was given were alive. Twelve died from metastatic disease, and 5 from the effects of x-ray therapy. Thirteen, or 46 per cent, of 28 patients with operable retroperitoneal metastases, who were also treated with deep x-ray therapy, were living; 10 died from metastatic disease, and 5 from the effects of irradiation. Of these 13 patients 8 had embryonal carcinoma, and 5 had teratocarcinoma.

These figures indicate the serious aspect of deep x-ray therapy in high dosage — a mortality of about 10 per cent — and the relative effectiveness of the combination of radical dissection of the retroperitoneal lymph nodes and deep irradiation. A five-year survival of 46 per cent seems extremely good. One may speculate about the 31 per cent mortality among patients who had retroperitoneal-lymph-node dissection without evidence of metastatic disease. It may be that primary metastasis to the contralateral lymph node was present and not recognized or that nodes above the level of dissection were involved and not removed. Lewis's dissection was done through an abdominal incision, which does not allow easy dissection above the level of the renal pedicles, and my own experience indicates that the thoracoabdominal incision,[91] carried out through the bed of the tenth rib extending toward the public tubercle, gives better exposure of the renal pedicle and subdiaphragmatic area. One is almost committed to bilateral retroperitoneal-lymph-node dissection in patients with radioresistant tumors if all is to be done for them that is possible. At least 1 death from metastatic disease developing in retroperitoneal lymph nodes on the contralateral side in the presence of negative nodes on the same side as the tumor has occurred at the New England Center Hospital.

The plan for treatment therefore seems to involve, first, earlier diagnosis and earlier exploration for questionable lesions of the testes; secondly, careful section of the tumor to determine its true pathological nature; thirdly, treatment of seminoma by radiation to the retroperitoneal, cervical and mediastinal areas by tumor dose somewhat over 2000 r; fourthly, bilateral radical dissection of the retroperitoneal lymph nodes for all patients with radioresistant cancer when metastatic disease is either not demonstrated or considered operable; fifthly, deep x-ray therapy if metastatic disease is found, but if none is demonstrated this treatment is to be withheld (at the New England Center Hospital deep irradiation is not given when only one or two positive nodes are found in an effort to determine whether testicular tumors with retroperitoneal metastases may be cured by surgery); and, finally, careful study of patients with adult types of teratoma since the diagnosis may be an error, as indicated by 2 of Lewis's 10 patients who died of metastatic disease. If evidence of retroperitoneal metastases develops dissection must be done. A much more aggressive surgical attack on these lesions seems indicated.

Cancers of the Glans Penis and Male Urethra

Cancer of the glans penis and male urethra beyond the membranous portion may be grouped for consideration of therapy. There seems little doubt that cancer of the prepuce and glans penis is related to chronic irritation beneath a tight prepuce, perhaps in association with the carcinogenic effect of retained smegma. Cancer of the urethra is also usually associated with long-standing inflammation, often stricture. For this reason any stricture that changes char-

acter — that is, becomes more difficult to dilate or becomes associated with a mass developing in the stricture area — should be carefully evaluated for malignant change. Unfortunately, many such cases are considered to be periurethral abscesses, and diagnosis is not made until it is too late for curative therapy.

Treatment must be based on the lymphatic drainage pattern since most of the tumors metastasize via local lymphatics to local nodes. Harlin[92] states that there are 3 lymphatic pathways from the penis and urethra: the prepuce, skin and subcutaneous tissue drain into the superficial inguinal nodes, some of which in turn communicate with the deep inguinal nodes; the glans penis and corpus cavernosum on each side drain into a plexus of anastomosing lymph vessels in front of the symphysis pubis — from this plexus lymphatic channels drain into the deep inguinal and external iliac nodes by way of the crural and inguinal canals; and the urethra and corpus spongiosum drain directly into the deep inguinal nodes along the external iliac vessels, following the course of the dorsal vein of the penis.

Treatment for cancer involving the glans and prepuce or glans with extension to the corpora may be local irradiation (with radium or x-rays), which has been favored in Europe, as evidenced by a report by Engelstad[93] concerning 72 patients, 64 of whom received primary radiation therapy. This was the only treatment given 37 apart from circumcision or dorsal slit. Because of recurrence electrocoagulation or amputation became necessary on 27 patients; 88.9 per cent of these who had no evidence of glandular metastases were alive and free of disease after five years. Patients with early lymph-node metastases were treated by groin dissection, and 65 per cent survived for five years. No patient with extensive metastases survived. These figures seem surprisingly good.

In this country, perhaps owing to the influence of Hugh Young and to poor results from radiation therapy, most cancers of the penis have been treated surgically. Hudson, Cason and Scott,[94] analyzed all cases at the Brady Urological Institute of the Johns Hopkins Hospital treated by the radical operation described by Hugh Young. This operation is a one-stage procedure performed through a curved incision made from one iliac crest to the other, the central portion being placed over the symphysis pubis, with incontinuity prolongation down over the dorsum of the penis as two parallel incisions terminating in the amputation incision about the shaft of the penis. Through this, aside from subcutaneous tissue left in contact with the skin flap, all tissue from the abdominal wall down to the rectus muscle and external-oblique fascia, including the superficial and deep inguinal lymph nodes, is removed. Amputation is performed sufficiently proximal to palpable cancer in the penis to provide a safe margin; 70 patients with proved carcinoma were operated on between 1907 and 1946, with a mortality of 7.1 per cent. Fifty-one patients were adequately followed. An over-all five-year survival of 45.6 per cent was found; about half the patients had metastases to the regional lymph nodes. The five-year survival of those with metastases was 31.5 per cent, and that of those without metastases 55.5 per cent.

This operation does not include pelvic-lymph-node dissection, which seems advisable. Hudson, Hopkins and Fish[95] recently described such an operation that includes an en bloc dissection through an incision similar to that of Young, in which, first, the penis is amputated 3 cm. proximal to the gross edge of primary lesion (frozen section to confirm amputation in a tumor-free area). This is followed by removal of dorsal-skin lymphatics and subcutaneous tissue of the penis for 2 cm. and of subcutaneous fat, fascia and lymphatics as deep as the anterior abdominal fascial sheath from the level of the umbilicus to a point 5 cm. below the saphenofemoral junction on each thigh (the dissection extends laterally just beyond the anterior superior iliac spine on each side). Finally, the inguinal, femoral, iliac and preaortic lymph nodes, areolar tissue, lymphatics and fat are excised.

One must concede that this is the most radical operation that can be done for cancer of the penis or urethra. Results will be awaited with interest.

An alternative procedure used by others and described recently by Kuehn and Robert[96] to accomplish essentially the same objective has been, first, to perform amputation of the penis, either partial or complete, depending on the extent of the local lesion. After healing and subsidence of local and lymphatic inflammation, which is frequently present, bilateral dissection of the inguinal and femoral iliac lymph nodes, with excision of all subcutaneous fat and areolar tissue between the base of the penis and the gland containing tissue, is done through two incisions beginning medial to each iliac spine and extending across Poupart's ligaments to points below the saphenous femoral junctions. After superficial dissection the external-oblique fascia and underlying muscles are incised and retracted to allow dissection of the iliac group of nodes. I have considered healing better after this operation than after the extensive operation of Young, which is usually associated with some skin slough and delayed healing.

The important considerations are that the disease remains local for a long time and that a vigorous attack is indicated. Radiation therapy for glandular metastases in most hands has been disappointing.

Cancer of the urethra in the male seems to require a similar method of therapy, though in early cases segmental resection and anastomosis of the urethra and corpus spongiosum may be warranted. In all large lesions, or those involving the bulbous urethras, radical excision as outlined above seems indicated. Lesions involving the triangular ligament and prostate require, in addition to complete amputation and gland

dissection, prostatovesiculocystectomy and ureteroenterostomy. Fortunately, such cases are rare.

Carcinoma of the Female Urethra

Cancer of the female urethra that involves the proximal or meatal portion may be treated by excision or radiation therapy with radium or deep x-rays or both. Fricke and McMillan[97] reviewed 35 cases treated at the Mayo Clinic from 1918 through 1942. Most lesions were in the proximal or meatal portion of the urethra although in some advanced cases the entire urethra was involved. Inguinal lymph nodes were involved in 26 of the 35 cases. Fourteen patients received radium therapy only, and 10 radium and x-ray therapy. In the others radium or radon and x-ray therapy was combined with excision or cauterization or both. Of 34 patients who could be traced 15, or 44.1 per cent, survived for five years or more after diagnosis and treatment. A critical analysis of such cases suggests that when the lesion is small and confined to the distal urethra, surgical excision and bilateral inguinal-lymph-node dissection is indicated. Lesions that are larger and involve the major portion of the urethra, including the bladder neck or vaginal wall, require a radical excision of the urethra, bladder, vagina and uterus as well as careful dissection of the pelvic and inguinal lymph nodes with ureteroenterostomy for real chance of cure. Lymphatics draining the distal urethra pass to the inguinal nodes whereas those of the proximal urethra and the bladder neck drain to the hypogastric and external iliac nodes.

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MEDICAL INTELLIGENCE

BY THE LONDON POST

Rehabilitation — Food Rationing in Retrospect — Foot Rot, Worms and Orf

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FULL employment and an enlightened social conscience are the two main contemporary factors that emphasize the importance of rehabilitating the disabled. The whole field of rehabilitation has recently been the subject of a Government survey, and a British Medical Association Committee has submitted its own views on the problem. This committee considered that 25 per cent of all patients passing through hospitals for the acutely disabled would benefit from planned rehabilitation. This must be an indivisible process by which the stages of acute illness, convalescence and resettlement merge into one another. Medical supervision continues to be necessary after active medical treatment has been completed, and at no stage short of complete recovery can the physician hand over responsibility to nonmedical personnel.

The Committee suggested that a resettlement clinic should be an integral part of all major hospitals and should be available to both general practitioners and hospital staffs. Such a clinic would be staffed by a consultant, a general practitioner, a social worker and a disablement officer. Psychiatric advice, as well as physical treatment, should be available. The patient's ability to work would finally be assessed by the medical staff in consultation with technical experts.

In recent years there have been a number of special experiments in rehabilitation — in particular the Papworth Village Settlement for tuberculous persons and the Austin Motor Company factory for disabled miners. Another venture was the formation of Remploy Limited in 1945. This was registered as a public corporation financed by Treasury funds under the Disabled Persons Employment Act of 1944. The object of the corporation is to provide employment for persons so severely disabled that they are unable to work under ordinary industrial conditions. Within seven years of its formation there were 90 Remploy factories, with 6000 employees. The disabilities included the effects of injury, arthritis, skin diseases, psychoneurosis, epilepsy and other organic nervous disorders.

Great problems confront the management of Remploy. Most of the workers are unskilled in the trades offered. Many have psychologic difficulties associated with their disabilities or with long unemployment. Some have lost the will to work, and others have acquired the old-soldier mentality, which seeks to do the minimum work for maximum pay. The goods manufactured by Remploy have to be carefully chosen. The work must be within the compass of the disabled employees, who must not be exposed to any new industrial hazard. Knitwear, cardboard-box making, light engineering and electric assembly work have all been successful projects. By trade-union agreement, Remploy workers receive three quarters of a full-time wage, although their output is only a third of the normal. It is not surprising that the corporation's annual account shows a heavy loss, but it must be realized that Remploy cannot compete on an equal basis with normal industry and experts agree that some financial loss is unavoidable. Against this must be set the fact that Remploy is continually returning workers to open industry and helping restore mental and physical health to disabled persons.

* * *

The derationing of food after fourteen years has been the occasion for general rejoicing. Ration books have been ceremonially burned, and housewives are now able to feed their guests on steaks without depriving their families or embarrassing the guests. Nevertheless, in retrospect, it may be questioned whether rationing was a bad thing. Under the impetus of dire necessity, research into the science of nutrition proceeded apace, and the ration scheme itself developed into a social service. All essential foods were available to every citizen in amounts necessary to maintain health, and provision was made for priorities. Expectant and nursing mothers, school children, young factory workers and workers in heavy industry were all allowed extra rations, and invalids requiring special diets were also granted concessions.

The national menu certainly became monotonous, and all dietetic luxuries disappeared. However, mothers and their children were healthier than before, and during the last year of war, the infant and maternal mortality rates reached record low figures. Furthermore, even in conditions of overcrowding in air-raid shelters, no major epidemic occurred. These facts in themselves testify to the work of the experts in nutrition, agriculture and economics who advised on the minimal diet required to maintain health and efficiency under war conditions.

It is hoped that with the lifting of the last restriction the nation will not now pass into a state of overnutrition and so give yet another boost to the already rising incidence of diabetes and atherosclerosis.

* * *

The weather men are now taking cover behind the fact that statistically this has not been the worst

summer on record. Nevertheless, during the two weeks' vacation that I recently spent on a Devonshire farm, the English summer did its worst — rain, rain and more rain.

The farmer was worried about his corn harvest and depressed about his sheep. Because of the damp ground, the sheep had developed foot rot, worms and orf. I was immediately on the alert when I heard that they had orf. I remembered being shown a case in a shepherd but had forgotten how the disease was transmitted. I was in the farmyard when the farmer and his shepherd gathered the flock together and separated those with orf from those without it. I soon spotted the lesions — pustular, impetiginous-looking areas of dermatitis, especially around the mouth. Nearly all the flock were affected; a veterinary surgeon confirmed the diagnosis and prescribed Propamidine cream. Next day, to my horror, I saw the farmer smear this cream over the faces of his sheep with his bare hands, and it was immediately clear how the disease could be transmitted to man, although the notion that it might be contagious seemed quite new to the farmer.

A day or two later I tactfully asked about the orf. The farmer reminded me that the veterinary had ordered "that new chemical cream from London," but his shepherd had heard from a neighboring farm that potash of permanganate was "the best stuff" and he was using this on half the flock. Here, indeed, was a therapeutic trial, half the sheep being treated with Propamidine cream and half with potassium permanganate.

The last day of my vacation the rain stopped and the sun shone, and again I asked the farmer about his sheep. This time he smiled and in broad Devon he said, "They be fine, we be putting them in for the Sheep Show next Saturday but only to please my shepherd because he thinks he's cured them with his potash!" A little later I met the shepherd, who announced "Sheep's better, Sir. Cured 'em with my potash. Us be going to put 'em in the Show on Saturday — but only to please the farmer because he thinks he cured 'em with that new chemical cream!"

The tragedy was that there was no control series! But, never mind, the farmer and his shepherd were happy and I only hope that neither (farmer nor shepherd) will develop any granulomatous lesions that could be orf.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40391

PRESENTATION OF CASE

First admission. A thirty-two-year-old woman entered the hospital because of a mass in the left breast, first noticed two weeks previously. Physical examination was within normal limits except for a freely movable mass in the left breast. A left radical mastectomy was performed, and pathological examination showed scirrhous carcinoma, with involvement of 3 of 22 lymph nodes. After an uneventful postoperative course the patient was discharged on the eleventh hospital day.

Second admission (ten months later). She had done well until six weeks before the second admission, when enlarged lymph nodes in the left side of the neck were found. X-ray treatment was given, with regression of the lymph nodes, but after completion of the treatment an additional enlarged lymph node was discovered in the right axilla.

Physical examination again was unremarkable, except for the presence of several firm lymph nodes palpable in the right axilla.

Roentgenograms of the chest, spine and pelvis showed no evidence of metastases.

Bilateral oöphorectomy was performed; the right axillary lymph node removed at the time of this operation revealed metastatic carcinoma. She left the hospital one week later.

Third admission (two months later). The patient had been reasonably well until three days before this admission, when severe generalized steady headache, vague "giddiness" (without true vertigo), generalized weakness and unsteadiness of gait developed. She also complained of blurring of vision, with oscillatory movements of objects as she looked at them. There was no nausea or vomiting, and no impairment of consciousness.

She was alert and co-operative with intact awareness and memory. A moderately large, firm lymph node was palpable in the right anterior cervical region. The general physical findings were otherwise unchanged. On neurologic examination the optic fundi were not remarkable, and the pupils were normal. There was marked nystagmus on lateral gaze in either direction, coarser and slower to the right than to the

left. The other cranial nerves were normal. Motor performance in the arms was within normal limits, but there was severe unsteadiness and impairment of co-ordination in the legs, somewhat worse on the left. Tendon reflexes were hypoactive in the left and normal in the right arm; the left knee jerk was considerably more brisk than the right; the ankle jerks were absent (they had been considered normal on previous admissions). The plantar reflexes were normal. There were no sensory abnormalities.

The temperature was 98.8°F., the pulse 94, and the respirations 20. The blood pressure was 110 systolic, 80 diastolic.

Routine blood and urine examinations were negative. Roentgenograms of the skull were within normal limits.

The patient's headache subsided in about five days with the aid of analgesic medication. Neurologic examination on the sixth hospital day showed greater severity of nystagmus than previously, with wide excursions, largely vertical, on looking to the left, and horizontal on looking to the right. There was moderate unsteadiness of the arms and severe ataxia of the legs bilaterally so that she was unable to place the heel on the knee. The right knee jerk was absent; the left was present; ankle jerks again were absent, and the plantar reflexes were normal. Three days later nystagmus was even more severe and about equal to either side, and ataxia of the limbs was even more severe than on the previous examination. The reflexes were as before, except that the left plantar reflex was now equivocal. Again, there were no sensory changes. The mental status remained normal.

She received estrogens and x-ray therapy to cervical lymph nodes, and was discharged on the thirteenth hospital day.

Fourth admission (six months later). Since discharge the patient had been unable to walk unassisted, but could use the arms for ordinary activities such as feeding herself. Blurring of vision had become somewhat worse. However, she had had very little headache, and reported that she had gained weight.

On general physical examination there were no new findings. No lymph nodes were now palpable. On neurologic examination she was mentally clear. There was greater ataxia of the arms than six months previously, but little change in motor performance otherwise. Marked nystagmus persisted. Tendon reflexes were unchanged. The right plantar reflex was now questionably normal, and the left doubtful or extensor. Sensory examination again was negative.

The temperature, pulse and respirations were normal.

Roentgenograms of the skull, chest, spine and pelvis showed what was interpreted as radiation pneumonitis in the left upper lobe, but no evidence of metastases. On lumbar puncture the spinal fluid was under a pressure equivalent to 170 mm. of water, was clear and contained no cells; the fluid had a protein of 41 mg. per 100 cc. and gave a colloidal-gold reaction of 1222110000.

X-ray treatment to a total of approximately 1100 r was given to the cerebellar region. On the eleventh hospital day, the patient was discharged.

Final admission (two months later). Her condition remained much the same for about a month, when right-upper-quadrant abdominal pain, anorexia, nausea and jaundice gradually developed. On readmission she was moderately icteric, with palpable lymph nodes in the right axilla and supraclavicular regions. The neurologic findings were as before. Her condition gradually deteriorated, and she died on the fourth hospital day, two years and eight months after the radical mastectomy.

Differential Diagnosis

Dr. F. A. Quadfasel*: I have been asked to discuss the neurologic aspects of this case.

The neurologic symptoms developed twelve months after the first admission for treatment of cancer of the breast. The patient complained of severe headaches, giddiness, general weakness, unsteadiness of gait and blurred vision, with oscillatory movements of objects, all of which had developed three days earlier. These movements, which had developed rather suddenly, suggest nystagmus. Congenital nystagmus or nystagmus of slow development or of long standing does not lead to blurred vision or movement of objects. The neurologic examination revealed nystagmus apparently more marked to the left, at least at first, that soon became bilateral. A vertical component was mentioned, but vertical nystagmus together with horizontal nystagmus has no specific localizing value. Only pure vertical nystagmus on upward gaze has a definite localizing value, indicating disturbance in the cephalic portion of Deiters's nucleus or in the collicular plate. There was also ataxia of both legs, more marked on the left than on the right. The reflexes were underactive in the left arm and the ankle jerks were absent. All these signs are referable to the cerebellum or cerebellovestibular pathways. The diminished tone resulting from a cerebellar lesion could explain the diminished reflexes. Although at the onset the signs were more marked on the left, pointing to a left-sided lesion, they soon became equal bilaterally. Little was said about dysmetria, adiadochokinesis and past pointing, but much about unsteadiness and inability to walk, which is associated with a lesion of the vermis. On the whole, one could perhaps state that the process progressed from caudal to rostral and from left to right. More detailed localization is always unsatisfactory. I remember a pa-

*Chief, Neurological Service, Boston Veterans Administration Hospital; assistant professor of neurology, Boston University School of Medicine.

tient with pineal metastases from carcinoma who had the same symptoms, together with brain-stem signs and remarkable cerebellar symptoms. The absence of all brain-stem signs and cranial-nerve involvement in the present case makes it rather unlikely, of course, that the lesion extended into the midbrain and the pons.

Since I am dealing with carcinomatosis, I must not forget that with it there may be a polyneuritis that may lead to diminished reflexes. The nerve roots may be involved by a so-called carcinomatous meningitis that may be present through the whole spinal canal. There need be no sensory disturbance or paralysis. The spinal fluid may be normal.

Although the left knee jerk was brisk, there was no weakness. The plantar reflexes were normal, and no pathological reflexes were mentioned. There was at this time no evidence of involvement of the pyramidal tract or of the sensory system. Even later, although nystagmus and ataxia were more marked, the only suggestive evidence of involvement of other than the cerebellar system was a doubtful or extensor plantar reflex on the left, noted during the fourth admission.

What was the cause of these signs and symptoms? The first consideration is metastatic tumor in the cerebellum, but I doubt that that would be the subject of the conference. Cerebellar metastases are the most frequent of the carcinomatous metastases to the brain from the breast. A tumor in that location, however, should have given rise to much more severe signs in a shorter time. The pia may be infiltrated with carcinoma, but that can only be recognized under the microscope; such a diagnosis is not usually made clinically. I must therefore examine other findings for hints of causation.

There was a minimal rise in temperature and pulse at the onset of these complications, but blood findings were within normal limits. The x-ray studies did not reveal any abnormalities. There were no electroencephalographic findings and no air studies to help me. There was no papilledema, altered state of consciousness or other localizing signs. Again, on the fourth admission the temperature, pulse and respirations were normal. The spinal-fluid examination was negative; a second examination was not done. A tumor in the posterior fossa may give rise to considerable increase in protein; however, if there had been increased intracranial pressure it would have been evidenced by erosion of the sella turcica or the clinical appearance of papilledema after more than six months.

This brings me to the course of the illness. There was a rather sudden onset, with headache and giddiness. Suddenness is not the common mode of onset of brain tumor but does not exclude it, and often occurs with metastases. Other conditions with sudden onset are hemorrhage into a tumor or cyst, an infection such as an early abscess, obstruction of the aqueduct and hemorrhage. The absence of all sensory disturbances excludes the occlusion of one of the cerebellar vessels. Moreover, the further course is against a vascular lesion and cerebellar apoplexy. The examination of the spinal fluid, the general symptoms and the white-cell count gave no evidence of an abscess. There was no source for an abscess, and there was no increase of the white-cell count and no elevation of temperature, although this need not be present. There are no data to support that assumption. Hemorrhage into a cyst would presume the presence of a hemangioma, but the facts do not indicate a condition of long standing. Moreover there were no eye signs to suggest Lindau's disease. An obstruction such as a developmental stenosis of the aqueduct should have led to repeated attacks of vomiting, to mental changes and possibly to other brain-stem signs. There was no history of streptomycin medication. Another feature to be discussed is the increase in severity of the same symptoms without involvement of other areas of the nervous system or signs of increased intracranial pressure. The severe headache, however, subsided after five days and seems to have been minimal thereafter. In the history there was no evidence of chronic progressive disease with remissions, nor was there multiplicity of findings. There is also a rare encephalitis of the cerebellar cortex, more often seen in children. I do not believe that the data allow me to make a definite diagnosis of any of the conditions listed.

Since I am forced to make a diagnosis on the basis of the material at hand I should prefer to consider a carcinomatous meningitis and a nonexpanding lesion of the cerebellum. One might add that the apparent retardation of development after the x-ray treatment suggests a radiosensitive process.

DR. BENJAMIN CASTLEMAN: Dr. Ayer, have you any comments?

DR. JAMES B. AYER: I wondered about metastases to the cerebellum and to the brain stem. The signs seem compatible with a brain-stem lesion, and my experience shows that this focus is commonly involved by metastases from breast cancer.

CLINICAL DIAGNOSES

Scirrhous carcinoma of left breast, with widespread metastases.
Cerebral metastases of carcinoma.

DR. F. A. QUADFASEL'S DIAGNOSES

Nonexpanding lesion of cerebellum.
Carcinomatous meningitis.

ANATOMICAL DIAGNOSES

Scirrhous carcinoma of left breast, with widespread metastases.
Subacute spinocerebellar degeneration accompanying extracerebral carcinomatosis.

Pathological Discussion

Dr. Castleman: At the time of autopsy we found, as was to be expected, an extensive carcinomatosis. Almost every organ, including parts of the intestines and gall bladder, was involved with carcinoma. Surprisingly enough, the bone marrow was not involved. Dr. Wheelock, have you any comment about the carcinoma of the breast?

Dr. Frank C. Wheelock: This patient illustrates how bad the prognosis in younger women with carcinoma of the breast so frequently is.

Dr. Castleman: The findings in the brain I shall leave for Dr. Richardson to describe.

Dr. Edward P. Richardson, Jr.: We are all indebted to Dr. Quadfasel for an especially interesting

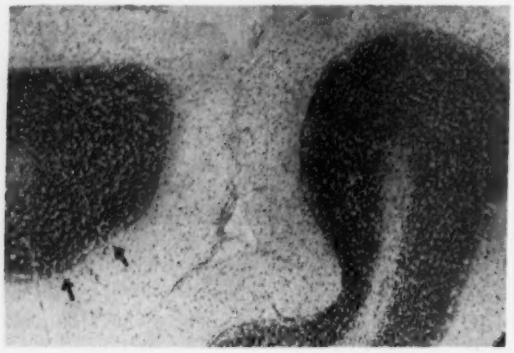

Figure 1. *Cerebellar Cortex (Note Almost Complete Absence of Purkinje Cells).*
A few remaining ones may be seen in the lower left corner (arrows). (Cresyl violet stain, low power.)

discussion of the neurologic aspects that were so prominent in this case. The difficulty that he had in ascribing metastatic carcinoma to this neurologic process was shared by those who followed the patient. Dr. Charles S. Kubik saw the patient a number of times and was impressed with the fact that although the cerebellar signs progressed to some extent, there was no evidence of involvement of the other parts of the nervous system or of increased intracranial pressure.

The brain and spinal cord were of generally normal appearance on gross examination, although the cerebellar folia were a little narrower and more prominent than usual. The whole brain was of average weight, but the cerebellum, removed from the brain stem after fixation, was considerably less than the expected weight for a brain of this size.

Microscopical examination disclosed no definite abnormalities in the cerebral hemispheres, including cerebral cortex and underlying white matter, thalamus, basal ganglions and subthalamic nucleus. In the cerebellum there was almost complete disappearance of the Purkinje cells to an approximately equal degree in all regions, although here and there occasional small groups of them were found (Fig. 1). The granule cells were not so numerous as normally, but there was no severe loss of these elements. Silver stains showed preservation of many, but not all, of the basket neurons, and numerous empty basket structures could be seen within which Purkinje cells were no longer present (Fig. 2). Stains for myelin sheaths revealed a considerable loss of myelinated fibers in the central white matter of the cerebellar folia and along the convex aspects of the dentate nucleus; fat stains disclosed numerous macrophages filled with fat droplets in these regions (Fig. 3), and Cajal silver stains showed a loss of axons commensurate with the degree of myelin destruction. The dentate and roof nuclei themselves were intact, as were the cerebellar peduncles.

Although there was very little clinically to suggest spinal-cord disease (except for reflex asymmetry and extensor plantar reflexes late in the course of the illness), sections of the spinal cord showed well defined fiber-tract degeneration in the posterior and lateral columns. These changes were most pronounced in the lumbosacral region, where there was striking fiber loss in the lateral and anterior corticospinal tracts and in the central portions of the fascic-

Figure 2. *Purkinje-Cell Layer of Cerebellar Cortex (Note One Intact Purkinje Cell Surrounded by Afferent Axonal "Basket" Structure).*
Next to it is an empty basket. (Cajal silver stain, high power.)

ulus gracilis bilaterally (Fig. 4). The tract degeneration decreased in severity in an ascending direction in the cord, so that in the cervical region there was barely any detectable change with myelin stains; fat stains, however, showed fat-laden macrophages in the fasciculus cuneatus and fasciculus gracilis bilaterally, lateral corticospinal tracts, dorsal and ventral

spinocerebellar tracts and anterior corticospinal tracts, clearly indicating involvement of those systems in the upper cord. Degeneration of the involved ascending fiber tracts could be found in the medulla oblongata but was absent in the pons; the corticospinal tracts were intact in the medulla and higher. In the diseased fiber tracts there was reactive astrocytic gliosis of a degree consistent with the amount of destructive change. The gray matter of the cord appeared intact. Spinal-nerve roots and available peripheral nerves were normal. These findings, therefore, indicate an intrinsic destructive process in the affected fiber systems, rather than secondary ascending or descending degeneration due to lesions above or below the levels represented in the sections.

There was no evidence of direct neoplastic involvement of any portion of the nervous system.

Thus the pathological changes were those of a rapidly advancing disease process chiefly involving the Purkinje cells of the cerebellum and their axonal extensions in the cerebellar white matter, and the long tracts in the spinal cord. The rapidity of the process was shown by the presence of considerable

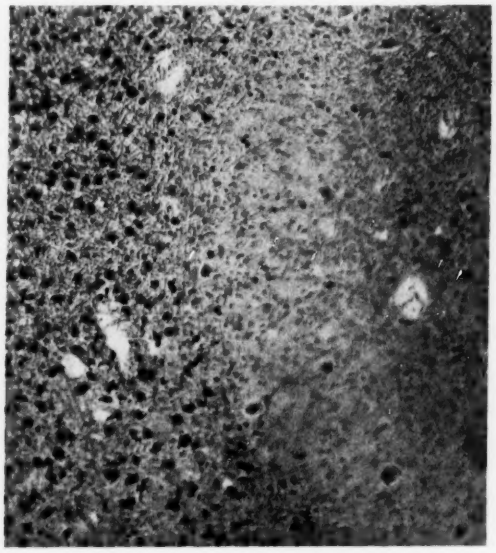

FIGURE 3. *Dentate Nucleus (Curved Pale Structure in the Center of the Photograph) with Large Numbers of Fat-Containing Phagocytes Surrounding It. (Oil Red-O Stain for Fat, Medium-High Power.)*

amounts of fat in the lesions described; this does not occur with slowly progressive disorders.

This case represents a very unusual neurologic complication of carcinomatosis. Only about 8 cases have hitherto been described in the literature in English,[1,2] and these have all presented a clinical and pathological picture closely resembling this. The primary site of the carcinoma has been in lung, ovary, or breast in these reported cases, and the neurologic symptoms and signs advanced rapidly in all, with a course of generally less than a year. Death usually resulted from the carcinoma, although several of the patients became helpless because of ataxia and a few became demented. A prominent feature in 6 of the 8 cases was the presence of lymphocytosis (up to about 100 cells) and elevation of protein (up to 450 mg. per 100 cc.) in the cerebrospinal fluid; at postmortem examination these cases showed striking

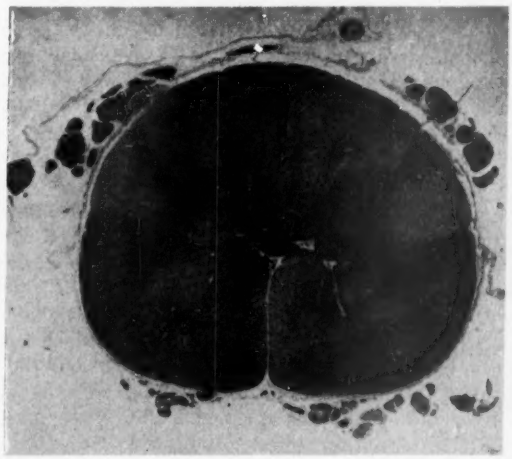

FIGURE 4. *Spinal Cord about the Third Lumbar Segment. Note loss of myelinated fibers (pale areas) in the posterior and lateral columns, and anteriorly in the region of the uncrossed pyramidal tract.*

lymphocytic infiltrations of the meninges and perivascular spaces.

We have as yet no idea about the etiology of this disorder. The conclusion seems inescapable, however, that it must have something to do with the presence of carcinoma.

DR. CASTLEMAN: Do you ever see this in the absence of carcinoma?

DR. RICHARDSON: With one exception, I have never seen the syndrome in the absence of carcinoma, and that was a case of rapidly advancing cerebrocerebellar degeneration in an elderly woman, with a total course of less than a year. In that case there was severe involvement of cerebral cortex, basal ganglions and cerebellum. We have seen a number of cases of cerebellar degeneration of similar pattern in older persons, with a chronic course of five to twenty years.

DR. CASTLEMAN: This patient did not die of the cerebellar disease; death was due to the carcinomatosis. The jaundice at the end was due to pressure of carcinomatous lymph nodes on the common bile duct.

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CASE 40392

Presentation of Case

A fifty-five-year-old chemical-laboratory worker entered the hospital because of abdominal pain.

The patient had been well until seven weeks previously when a "cold" with general malaise, nausea, occasional vomiting, diarrhea, fever (a temperature of 101.6°F.), cough and intermittent pain in the right upper abdomen radiating through to the back developed. Two days later, he was given penicillin intramuscularly after which he felt better except for the abdominal pain. He had had no jaundice, hunger, pain or tarry or clay-colored stools. Since childhood, he had had indigestion and had always taken a good deal of soda or Bisodol. He could not tolerate fried food. One week after the onset of the present illness, when low-grade fever and vomiting recurred and the abdominal pain worsened, he entered another hospital. At this time the temperature had returned to normal. Physical examination there revealed tenderness in the right upper quadrant of the abdomen on deep inspiration; the abdomen was soft, and there were no abnormal masses. The blood pressure was 140 systolic, 90 diastolic, the hemoglobin 15.2 gm. per 100 cc., the red-cell count 4,700,000, and the white-cell count 15,800, with 76 per cent neutrophils. Urinalysis was negative. The icteric index was 5.8, and the serum amylase 18 units per 100 cc. The blood Hinton test was negative. Cholecystogram revealed nonvisualization of the gall bladder, and an upper gastrointestinal series showed no organic lesion; the esophagus appeared normal on fluoroscopic examination. On the third hospital day cholecystectomy and appendectomy were performed. The gall bladder contained many minute yellow stones but appeared normal otherwise. Postoperatively, the patient vomited frequently, the pain persisted and leukocytosis continued. The wound broke down on the eleventh postoperative day, and was repaired after another exploration of the abdomen that proved negative.

He was discharged three weeks after the operation. At home he remained afebrile but continued to experience intermittent pain in the right upper abdomen, occasionally radiating to the back, downward to the periumbilical region and upward to the shoulders; it was now unrelated to food and was slightly relieved by external heat and soda. For three weeks, he had been anorectic and nauseated, had eaten very little and had vomited occasionally. He gradually became aware of feeling "a lump in the throat" that made swallowing increasingly difficult, especially of liquids that regurgitated without his gagging or retching. He also noted an increased amount of phlegm, but no cough until the day of admission, when he began to have a slight cough productive of a fair amount of frothy sputum. On the morning of admission he produced some dark chocolate-colored material that he felt had come from the upper abdomen. This had occurred once or twice since then. For the last few weeks he had taken no medicine, had eaten very little and had lost 25 pounds of weight. There was no history of cardiovascular, respiratory or urinary symptoms.

Physical examination revealed a well developed, wasted and chronically ill man lying flat in bed but preferring to lie on the right side. He had periodic hiccup, retching and cough. There was no mass in the neck; the trachea was freely movable; there were coarse rales at the lung bases; the heart was normal, and the abdomen was scaphoid without masses, palpably enlarged organs or tenderness. The left brachial and radial pulses were weak, but the left hand was warm.

The temperature was 98°F., the pulse 76 and the respirations 17. The blood pressure was 100 systolic, 70 diastolic, in the right arm, and 80 systolic and an unmeasurable diastolic in the left.

Urinalysis was negative. Examination of the blood disclosed a hemoglobin of 8.7 gm. per 100 cc. and a white-cell count of 23,800, with 89 per cent neutrophils, 2 per cent young neutrophils, 7 per cent lymphocytes, 1 per cent monocytes and 1 per cent basophils. The serum total protein was 5.7 gm., and the nonprotein nitrogen 25 mg. per 100 cc., the sodium 128 milliequiv., the potassium 3.7 milliequiv., the chloride 87 milliequiv., and the carbon dioxide 28 milliequiv. per liter. The prothrombin time was 16 seconds (normal, 13 seconds). A stool was guaiac negative. An electrocardiogram revealed a normal rhythm at a rate of 95, with occasional atrial and ventricular premature beats, a PR interval of 0.16 second, a QRS interval of 0.06 second, and a normal axis; the T waves were upright in Leads 1, 2, 3, aVF, V_3, V_4, V_5 and V_6; the ST segments were slightly elevated in Leads 2, 3 and aVF; and the complexes were slightly M-shaped in Leads V_1, and V_2.

A roentgenogram, together with fluoroscopy and barium-swallow examination, revealed a well circumscribed, homogeneous, rounded mass in the medial aspect of the left side of the chest within the mediastinum, that could not be separated from the aorta. It had compressed and displaced the esophagus toward the right causing almost complete obstruction (Fig. 1). The mass did not pulsate fluoroscopically. Both leaves of the diaphragm moved, but the right moved more freely than the left. The lung fields were moderately emphysematous. A triangular-shaped density with its apex pointing laterally was also seen in the mediastinum superimposed over the mass. A round density was also seen to the left side of the mediastinum just above the aortic knob. A film after four hours showed essentially the same amount of barium as on the first examination in the upper esophagus above the mass. The posterior wall of the trachea was compressed and flattened with narrowing of its lumen to about 5 to 6 mm., just above the bifurcation. A roentgenogram of the abdomen showed that the tip of the right lobe of the liver extended to the iliac crest. Renal and psoas-

muscle shadows were not remarkable. A few flecks and streaks of calcific density were seen to the right side of the lower lumbar spine, probably vascular calcifications. The bowel was not abnormally distended. The bones were somewhat demineralized. A roentgenogram of the chest repeated on the last hospital day did not reveal any significant change in the over-all size of the mediastinal mass. Its posterior border was not as distinct as on the previous films. There was increased narrowing of the trachea. No fluid was recognized in the pleural spaces.

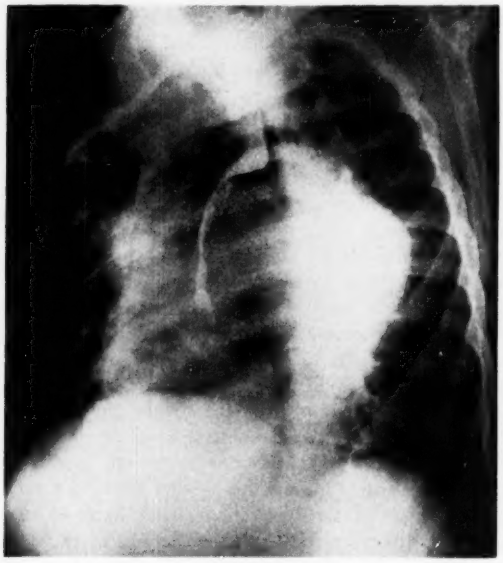

FIGURE 1. *Left Anterior Oblique View of the Chest. The left mediastinal mass causes displacement of the esophagus anteriorly. Esophageal obstruction is present 7 cm. from the dome of the diaphragm.*

The patient ran a low-grade fever with the temperature ranging between 99 and 100°F.; the pulse varied between 80 and 120, and the respirations between 20 and 30. He continued to have considerable pain in the upper abdomen, chest and arms, and coughing up of a large amount of thick mucoid sputum, with slight dyspnea and wheezing. The left radial pulse became absent. Hoarseness developed and the left vocal cord was completely paralyzed. Through a laryngeal mirror, a gray mass was noted in the trachea that was thought to be either mucus or neoplasm. On the fourth hospital day the patient suddenly coughed up or vomited 300 or 400 cc. of bright-red blood and became unresponsive, pulseless and pallid. The respirations ceased. Clotted blood was found in the trachea when the airways were cleared. During manual artificial respiration the patient died.

DIFFERENTIAL DIAGNOSIS

DR. J. WALLACE ZELLER*: The most striking findings on admission were those in the x-ray films and the history of rapid progression of the illness. One can only speculate concerning the initial symptoms — that is, the right-upper-quadrant pain, nausea, vomiting, diarrhea and fever. The location of the pain and the physical signs certainly pointed to the liver or gall bladder. Since the removed gall bladder revealed no evidence of cholecystitis, the possibility of a diffuse hepatic disease becomes more definite. This could have been either infectious or toxic in nature. According to the history, during the four weeks before admission to the hospital serious respiratory disease developed along with evidence of involvement of the esophagus. The x-ray examination of the abdomen revealed definite enlargement of the liver; however, on physical examination at admission it was not noticed. Four weeks previously a negative exploration of the abdomen was described, which must have meant that the hepatic enlargement occurred during the four-week period. A serious anemia appeared and there was striking loss of weight. Evidence of extrinsic pressure on the trachea, esophagus, left subclavian artery, left recurrent laryngeal nerve and possibly the left phrenic nerve was found. The production of dark chocolate-colored material on the morning of admission is of importance; it was either coughed up or vomited. It seems quite likely that the bright-red blood that was raised terminally came from the trachea. The extent of the bleeding suggests the rupture of a large vessel into the trachea.

An attempt to arrive at a diagnosis must take into account first of all the rapid progression of the illness and, secondly, the possible association between the original abdominal and later mediastinal manifestations.

At this point, it would be well to have a comment on the x-ray films.

DR. JOSEPH HANELIN: The chest films have a rather dramatic appearance, and show the presence of a large mass, which appears to be clearly within the mediastinum. The mass projects rather prominently toward the left and posteriorly. The esophagus is displaced considerably toward the right and somewhat anteriorly, and there is marked narrowing of the esophagus about 7 cm. above the diaphragm although a small amount of barium does trickle through (Fig. 1). The heart itself is not appreciably increased in size. Films taken on two subsequent days and more heavily exposed show the reflection of the posterior mediastinal pleura on the left assuming a triangular pattern at the level of the lung root. In addition to the larger mass that I have described, there is a smaller, 3-cm. rounded density lying above the aortic arch on the left. Even three days after the patient was first seen and given a swallow of barium some of it remains within the esophagus. The lung fields are essentially clear although there may be some engorgement of vessels near the lung roots. There is no increase in pleural fluid. The abdominal film does not provide much information. The question of whether

*Associate physician, Massachusetts General Hospital.

the liver is enlarged is not at all definite. The protocol merely states that the right lobe of the liver extends to the iliac crest. A prominent right lobe of the liver does not necessarily indicate pathologic liver enlargement. A few flecks of calcification lie to the right of the lower lumbar spine; their precise significance is not certain.

DR. ZELLER: Were there fluid levels in any of the masses?

DR. HANELIN: No; I am unable to see any fluid levels.

DR. ZELLER: How far down does the mass extend?

DR. HANELIN: It may well go down to the level of the diaphragm.

DR. ZELLER: This large shadow is made up of heart and what else?

DR. HANELIN: It is made up primarily of the mass, which cannot be separated from the aorta, and partly of the heart shadow.

DR. ZELLER: Is there any evidence from the films that there may be penetration of the diaphragm?

DR. HANELIN: I see no evidence of diaphragmatic penetration such as herniation.

DR. ZELLER: Before embarking on any further discussion I should like to inquire about some other data, which if in the record, may be helpful. Were any blood cultures done that were reported before the patient died?

DR. BERNARD M. JACOBSON: No.

DR. ZELLER: Was the sputum cultured or examined for amebas?

DR. JACOBSON: No.

DR. ZELLER: Were the stools cultured or examined for amebas?

DR. JACOBSON: No.

DR. ZELLER: Was there any evidence of exposure to specific toxins? The patient was a chemical-laboratory worker.

DR. JACOBSON: No. That was investigated very carefully by Dr. John Angley. The patient worked in the shipping department and was not handling the chemicals.

DR. ZELLER: Did he travel outside New England?

DR. JACOBSON: No.

DR. ZELLER: When I first read this history it seemed to me that salmonella infection might explain at least part of the picture. I wondered if the unusual mediastinal signs could have been produced by a large mycotic aneurysm of the aorta and metastatic abscess formation in the mediastinum. In salmonella infection, as in typhoid-fever infection, the commonest cause of right-upper-quadrant symptoms is cholecystitis, which was not present in this patient. Focal necrosis of the liver is described in the septicemic form of salmonella infection. One objection to this diagnosis is the absence of leukopenia in either of the two blood counts. Possibly at the time the counts were made, the complications had altered a leukopenia previously present. Although I cannot rule out the possibility I do not consider it as likely as another infectious disease to be discussed later. Tuberculosis has to be mentioned but there is little to help with a definite diagnosis.

The possibility of a toxic hepatitis associated with infection has to be considered. The absence of jaundice and the evidence favoring hepatic enlargement rather than a small liver make that unlikely.

Metastatic carcinoma of the liver and mediastinum is a possibility, as is lymphomatous involvement of these areas. Although the course seemed too rapid, an added mediastinal infection would make them possibilities. Since the x-ray films revealed a lesion of the mediastinum that could have been an aortic aneurysm, syphilis should also be mentioned. The rapid downhill course rules against this diagnosis; also, the blood Hinton test was said to have been negative six weeks before admission to this hospital.

The dark chocolate-colored material that may have been coughed up suggests the anchovy-sauce sputum characteristic of the rupture of amebic abscess of the liver into the lung. Usually, when this occurs the abscess perforates the right leaf of the diaphragm and enters the right lung. In this patient the right side of the diaphragm moved better than the left, and the involvement appears to have been principally mediastinal. I do not know if this could occur from direct rupture of an amebic abscess into the mediastinum. Proved cases of hematogenous spread of amebas to the lung, resulting in abscess formation, have been described. In looking up this subject I found a reference to cases of amebic pericarditis.[1] Most of these followed direct rupture of hepatic abscesses in the left lobe of the liver, but in rare cases hematogenous spread to the pericardium may have occurred. Amebic infection in the mediastinum could lead to erosion of blood vessels or actual aneurysm formation. An amebic abscess or an aneurysm could have produced the pressure on the trachea and esophagus seen in the x-ray films and led to final rupture into the trachea, with death from hemorrhage.

Numerous cases of amebic hepatitis and amebic abscess of the liver have been reported in the temperate zone. Often, no serious preceding intestinal symptoms had been observed. The type of pain and tenderness described in this patient, the irregular fever, enlarged liver, if it existed,—I am in doubt about that since Dr. Hanelin showed the x-ray films,—leukocytosis and absence of jaundice would be consistent with the diagnosis. I believe the earlier phases of this patient's illness are best explained on that basis. I admit that the mediastinal involvement is unusual.

DR. JACOBSON: Don't you think an amebic abscess would have been discovered at the time of the exploration?

DR. ZELLER: He may have had an amebic hepatitis then and the abscess may have formed later.

My first diagnoses are amebic hepatitis, amebic abscesses of the liver and mediastinum, with pressure on

the trachea and esophagus, and death from hemorrhage into the trachea.

DR. ALFRED KRANES: I was just whispering to Dr. Lerman about the striking similarity between this case and one of a dissecting aneurysm of the aorta that I saw recently; my patient's gall bladder was also removed. The type of pain was similar except that the interval between the cholecystectomy and the terminal event was longer in the case under discussion.

DR. ZELLER: It reminded me of a case of mycotic aneurysm due to salmonella infection that I discussed here last year.[2] That is why I mentioned that first.

DR. JACOB LERMAN: How would you explain the large mass above the aorta?

DR. ZELLER: That would be another amebic abscess.

DR. BENJAMIN CASTLEMAN: Do you think this man had a dissecting aneurysm, Dr. Kranes?

DR. KRANES: Yes. I did not have a chance to read this protocol carefully, but on the basis of Dr. Zeller's remarks I think it would be entirely consistent with a dissecting aneurysm.

DR. ZELLER: Where would the dissection have started?

DR. KRANES: Ninety per cent of dissections start in the thoracic aorta and give pain in the upper abdomen. In the patient I mentioned the dissection did not go below the diaphragm; yet most of the pain was localized to the right upper quadrant. The gall bladder was removed and happened to be full of stones; therefore, for a few days we were satisfied that we had solved that man's problem.

DR. FARAHE MALOOF: Did that patient have fever and jaundice?

DR. CASTLEMAN: He had no jaundice.

DR. LERMAN: I do not recall any dissecting aneurysm that paralyzed the vocal cords, presumably because of pressure on the recurrent laryngeal nerve. It is the ordinary syphilitic aneurysm that involves the recurrent laryngeal nerve at this point.

DR. CASTLEMAN: That is true. The reason for that is that most dissecting aneurysms do not result in a large saccular bulge that involves the nerve. An occasional dissecting aneurysm produces a medial hematoma sufficiently large to cause a bulge. I do not believe I have heard of a dissecting aneurysm that produced paralysis of the recurrent laryngeal nerve.

DR. JACOBSON: How do you account for the fact that in the outside hospital the blood hemoglobin was 15 gm. and on admission it was 8.7 gm. per 100 cc.?

DR. ZELLER: On the basis of my diagnosis, I should account for it partially by the anemia of infection. Also, when he came in he coughed up some dark-chocolate-colored material; that means he could have been bleeding.

DR. JACOBSON: Where was he bleeding?

DR. ZELLER: I assume from the trachea; the blood could have been vomited. We are not given that information. I do not even know whether the bright-red blood that he brought up at the end was from the trachea; he could either have vomited or expectorated it.

A PHYSICIAN: Was there any evidence of varices or thickening of the esophagus?

DR. HANELIN: No; there were no varices in the esophagus.

A PHYSICIAN: Was a Levin tube inserted?

DR. JACOBSON: Yes, postoperatively.

A PHYSICIAN: Do you think that might have caused some erosion?

DR. CASTLEMAN: That certainly does occur.

Dr. Jacobson, will you tell us about the opinion on the ward?

DR. JACOBSON: When the surgeon who explored the patient in the outside hospital entered the belly he knew he had not made the proper diagnosis; the small bits of gravel in the gall bladder could not possibly have accounted for the symptoms. When the patient entered this hospital he was quite sick. Our thoughts ran over a few of the possibilities that Dr. Zeller has mentioned, but we did not seriously consider diseases such as amebic or salmonella infection. It looked to us more like an erosion of the esophagus with a mediastinal abscess or possibly trauma from a tube. We also considered the possibility that this was a primary mediastinal tumor. Dr. H. Thomas Gephart thought it might have been an aneurysm especially with the drop in the hemoglobin. On admission the blood smear was consistent with blood-loss anemia. We had planned an angiogram, but when Dr. Gephart saw him that morning, it was obvious that he was in no condition for an angiogram. It was fortunate that Dr. Gephart decided against it because the patient died that afternoon.

CLINICAL DIAGNOSIS

Rupture of aneurysm of thoracic aorta.

DR. J. WALLACE ZELLER'S DIAGNOSES

Amebic hepatitis.
Amebic abscesses of liver and mediastinum.
Hemorrhage into trachea.

ANATOMICAL DIAGNOSES

Arteriosclerotic aneurysms of aorta, with rupture and massive hemorrhage into esophagus and posterior mediastinum.
Arteriosclerotic aneurysm of left subclavian artery.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The manner in which the patient died led the clinicians to make a final diagnosis of a ruptured aneurysm.

At the time of autopsy we found that he did have a rupture of an aneurysm. He had, however, more than one aneurysm. There was one in the left subclavian artery, which Dr. Hanelin tried to point out on the

x-ray films; it was a saccular arteriosclerotic aneurysm with a mouth that was quite large. The aneurysm was thick-walled and somewhat calcified. Most of the descending thoracic aorta was huge and had pushed the esophagus to the right; this huge bulge proved to be an aneurysm of the aorta about 12 cm. in length (Fig. 2). Terminally, it had eroded into the esophagus, and at autopsy the esophagus was full of blood,

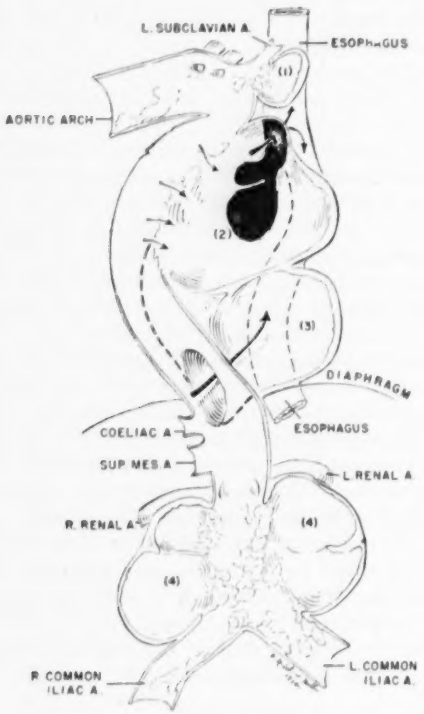

FIGURE 2.

as was the entire stomach. This aneurysm had also ruptured anteriorly into the mediastinum so that there was a large amount of clotted blood in the posterior mediastinum that had dissected down along the spine. This aneurysm did not communicate with the one in the left subclavian artery but it did communicate with another aortic aneurysm, which was located for the most part just above the diaphragm, although its mouth was below the diaphragm. I believe it was this lower aortic aneurysm that caused the gallbladder type of pain. Although I had expected to find celiac-axis involvement to explain the pain, we found no occlusion of the celiac axis. I should have mentioned that the recurrent laryngeal nerve and the vagus were compressed by the mediastinal aneurysm. Below the renal artery was still another large aneurysm—larger than the one lying above. I believe the calcifications that you observed on the x-ray films, Dr. Hanelin, were in the wall of the arteriosclerotic aneurysm. Both iliac arteries were also markedly dilated.

This case, then, is an example of multiple arteriosclerotic aneurysms. Dr. Si Chu Ming, who performed the autopsy, was very careful to rule out a dissecting aneurysm at the time of autopsy. He demonstrated that the aneurysms were definitely separate and that the aorta between the aneurysms was perfectly normal. Also, the elastic-tissue stains showed that the hemorrhage was in the adventitia; hemorrhage in all dissecting aneurysms occurs within the media. This man was quite young to have had multiple arteriosclerotic aneurysms; ordinarily, they occur in patients in the seventies.

DR. KRANES: What caused the fever and right-upper-quadrant pain?

DR. CASTLEMAN: I doubt if we could prove that any of the aneurysms were infected, but there were many mural thrombi—some recent and some obviously older—in the aneurysm. We found no evidence of any infectious process anywhere.

A PHYSICIAN: Was the liver enlarged?

DR. CASTLEMAN: It was not enlarged; it weighed 1800 gm.

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SMOKING, CANCER AND HEART DISEASE

ALTHOUGH the *Journal* has been an early champion of those who have insisted that the cigarette-cancer "controversy" be studied soberly and not dismissed out of hand, the time has come to point out weakness in the argument of those who regard the aromatic distillate as a wholly deadly venom. Recently, smoking has once again been linked to cancer of the lung,[1] — but this time also to heart disease, — and the evidence has been widely disseminated through the press and in *Time*[2] and *U.S. News and World Report*.[3] Since the public's concept is determined by the facts given in lay periodicals it is pertinent to review the most recent chapter of the story as it is presented in two weekly magazines.

Time's summary of the cancer evidence — "On the question which had started the whole ruckus 'Does Cigarette smoking eventually cause cancer' the statisticians had to hedge" — is over simplified. To pose the question that way is like resting an all-or-none case against liquor on whether or not it eventually causes cirrhosis of the liver, or against water on whether or not it sometimes causes drowning. To create a yes or no dichotomy is to ignore such important factors as constitutional susceptibility and smoking habits — that is, dosage of carcinogen. Only the most ardent of medical evangelists would try to maintain the hypothesis that the moderate smoking of cigarettes causes cancer; drenching the bronchial mucosa regularly in a tarry distillate is evidently a different matter.

The newly assembled statistical evidence of an association between smoking and deaths from heart disease needs thoughtful reappraisal before too much is made of it. The first obligation is to consider whether nonsmokers are not subjected to lesser cardiac risks than smokers. Do people with different occupations have different smoking habits? If they do, differing morbidity experience may represent job differences rather than smoking differences. For example, cardiac morbidity from coronary-artery disease among sedentary motormen was greater than morbidity among peripatetic bus conductors in Great Britain; this matter was recently treated editorially in the *Journal*. Similarly, if high-pressure, sedentary careers carry greater risks of coronary thrombosis than active trades and if people smoke more heavily when under sedentary job tensions, a relation between occupation and smoking will clearly exist to confuse any association that needs to be tested between heart disease and smoking.

The significance of some of these secondary associations has already been tested with smoking and cancer of the lung, and the results have been consistent with a cause-and-effect relation. For example, dusty and irritant trades were found to have an accessory influence on bronchogenic carcinogenesis; thus, heavy smokers who were also steamfitters or welders were found to have a worse experience than their fellows who were light smokers.[4]

The evidence of an etiologic association of smoking and lung cancer is older and more detailed and depends on a more sharply defined clinical entity and on more dramatically rising death rates than that bearing on smoking and heart disease. It is difficult to conceive that young people who are disciplined enough never to have smoked should have the same natural mortality as those who use the weed. In all likelihood not as many of the abstemious group allow themselves to overeat, overwork, overdrink, overspeed and the like. These secondary differences may well have a more significant influence on the heart than the lungs; at least it is difficult to see why the two groups should experience naturally great differences in mortality from cancer of the lung.

It may be freely hypothesized that the subtle fumes may be accomplices to the genesis of heart disease. However, it is more easily conceivable that a spurious correlation exists between smoking and heart disease than between smoking and lung cancer. If a sedentary, intensive occupation like that of the physician carries with it greater risks of coronary occlusion than an active, more relaxed occupation like that of the carpenter or bus conductor, this fact must be allowed for in attempts to test the effect of smoking on heart disease.

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STREPTOMYCIN-RESISTANT TUBERCLE BACILLI AS A PUBLIC-HEALTH HAZARD

It has been anticipated that the increasing numbers of patients in whom streptomycin-resistant tubercle bacilli persist in the sputum after treatment with streptomycin might create a serious public-health problem. Furtos and Doane[1] reported the case of a nurse who had been exposed to patients under treatment with streptomycin for tuberculosis and who subsequently, in 1947, contracted active tuberculosis; her gastric washings were found to contain tubercle bacilli resistant to 1000 microgm. of streptomycin per cubic centimeter before she herself had received any treatment with this drug. A similar case occurring about the same time was described by Brennan and Wichelhausen[2] in a hospital attendant from whom tubercle bacilli resistant to 100 microgm. per cubic centimeter were grown from a pleural fluid that was drawn before the patient had been given streptomycin treatment. This attendant had had a prolonged exposure to a patient with miliary tuberculosis in whom bacilli had increased in resistance to 500 microgm. per cubic centimeter during streptomycin therapy. Furtos and Doane failed to demonstrate streptomycin-resistant organisms in any of 385 other patients with tuberculosis before instituting streptomycin therapy.

In 1951 Ferebee and Appel[3] presented the results of a co-operative study on streptomycin-resistant tubercle bacilli undertaken in several sections of the United States. They found that 55 per cent of 157 patients who had been treated with streptomycin for three months had sputum positive for tubercle bacilli at the end of fifty-three weeks; the organisms in two thirds of these patients were resistant to streptomycin. The resistance of the tubercle bacilli tended to persist, although reversion to streptomycin sensitivity was observed in cultures from about 18 per cent of the patients. During the course of that study 18 other patients were encountered whose initial cultures yielded tubercle bacilli that were resistant to streptomycin; only 5 of them had previously been treated with the antibiotic.

Similar findings have been reported in children under thirteen years of age by Wilking and his coworkers[4] at Bellevue Hospital. They demonstrated tubercle bacilli resistant to 10 microgm. of streptomycin per cubic centimeter in 12 of 59 patients after streptomycin treatment had begun and also in 5 of 115 patients before any streptomycin had been given. The source of the infection in the children with organisms initially resistant to streptomycin was not discussed.

Recently, Thomas and his associates[5] described 9 cases in which drug-resistant tubercle bacilli were obtained although the patients had had no previous chemotherapy with the relevant drug. The organisms showed primary resistance to streptomycin in 4 of these patients, to para-aminosalicylic acid in 4 others and to both drugs in 1. The infection in 3 and possibly 4 of these patients was known to have been present before the drugs had come into general use; the original bacilli in these cases were therefore assumed to have been drug sensitive, and it was thought that the patients were subsequently superinfected with resistant bacilli.

A more thorough study of the prevalence of streptomycin-resistant tubercle bacilli was reported by Cummings and Livings,[6] who analyzed the results of streptomycin sensitivity tests in 5526 consecutive admissions to 30 hospitals over the seven months from May to December, 1953. Among the patients in their study who had previously received streptomycin therapy and who now yielded tubercle bacilli that were tested for sensitivity 20.4 per cent had organisms that were completely resistant to 10 microgm. of streptomycin per cubic centimeter. A careful review of the data in 1166 who had never received streptomycin therapy indicated that only 30, or 2.6 per cent, yielded tubercle bacilli completely resistant to 10 microgm. of streptomycin per cubic centimeter. Of the 30 patients, 9 had been in tuberculosis hospitals after 1946, and 4 had family contacts with tuberculosis patients after 1946, when streptomycin became generally available.

These findings suggest that exposure of patients in tuberculosis hospitals presents a likely source of infection with streptomycin-resistant tubercle bacilli. From all these observations it may be concluded that infection with streptomycin-resistant tubercle bacilli may occur particularly as a result of prolonged hospital exposure, but that this has not proved to be a serious public-health hazard.

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DEATH ON THE PLAYING FIELD

Injuries incurred as a result of competitive athletics are of such importance in the study and treatment of trauma as to constitute practically a surgical specialty. Deaths, however, figures on which have been compiled and analyzed by the statistical department of the Metropolitan Life Insurance Company, are relatively rare.

During 1951 and 1952, for example, only 11 deaths resulting directly from competitive sport occurred among the millions of males from age ten to age twenty-nine holding Metropolitan industrial policies. Of all the accidental fatalities occurring in this group, in fact, less than 1 in 300 could be so attributed. An analysis of the 11 shows that 4 resulted from participation in baseball and softball, 3 from golf, 2 from basketball and 1 each from football and track.

Material gathered from other sources indicates that New York City over a period of more than thirty years has averaged only 3 deaths annually from competitive sports and that there has been no fatality in major-league baseball since 1920 or in major-league hockey since 1937. A fatal injury has yet to occur in a game of professional basketball or in roller derby, which came over the horizon as a professional sport in 1935. The only death that has occurred in forty years during a soccer game resulted from a heart attack.

Baseball, only on account of the numbers playing it, is assumed to be the major killer, although football and boxing probably incur the highest rates. Thus, despite the fact that only a single death occurred in two years among policyholders, 65 direct and 29 indirect deaths were attributed to football in the five-year period from 1949 through 1953. Interestingly, high-school football with 37 direct deaths among the 600,000 players had approximately the same death rate as college football with 4 deaths occurring among 65,000 players. During the same period 9 deaths took place among professional and semiprofessional players and 15 among sandlot players, the numbers participating not being given in either case. Also during the same period, 12 deaths were recorded among the 3000 professional boxers and 17 among amateurs.

It is impossible to compare rates of fatal accidents in organized sports, where the numbers of participants can be estimated, with those occurring in playground and sandlot competition. Such an analysis would be of interest, as would a comparison of the secondary deaths among selected and trained athletes and those occurring among casual participants.

Injuries, illnesses and psychic trauma resulting from such a universal addiction to athletic activities will also bear greater and continued scrutiny. In this respect it is well known that careful selection of players and adequate graded training will reduce the injury and morbidity rate. Many school physicians who have given thought to the matter now attempt to curb the exuberance of muscle-conscious coaches who would sacrifice the frames of loose-jointed adolescents to the glory of the game and have been known even to tog out the lesser tots in uniforms that weigh almost as much as their wearers.

GREAT EXPECTATIONS

The statisticians of the Metropolitan Life Insurance Company are trained and accustomed to trip lightly through maze-like sets of figures over which others merely trip. Important, pleasant to study and not too complicated are those relating to the increasing length of life in the United States.

Based on the experience in 1951 the average duration of man's corporeal grip has increased to a new high of sixty-eight and five-tenths years—a gain of approximately twenty years since the beginning of the dynamic twentieth century. Obviously, the improved expectation has been greatest in the younger ages, since the infant mortality affects so greatly the over-all picture of life expectancy; in 1900, 1 in 8 newborn infants failed to live out its first year, whereas only 1 in 8 of those born in 1951 will fail to achieve its fiftieth birthday.

Bearing some remote resemblance to the half lives of isotopes, any person at any age has some sort of life expectancy; the younger he may be the better are his chances for living a considerable number of years, although, paradoxically enough, the enfeebled old dotard of ninety-nine has an infinitely better chance of reaching the century mark than has the most robust one-year-old.

To return to more precise figures, eleven years have

been added to the average life expectancy at age five, nine years at age twenty, and five years at age forty. Even at age sixty-five two and three-tenths years have been added to the former expectation, with the result that the average man of sixty-five can expect thirteen additional years, and the average woman fifteen and a half. Once the perils of infancy are passed seventy-one years is the average term of life, and for those who have passed fifty, three quarters of a century is a reasonable expectation—bar hell and high water.

Douglas Jerrold, in some remarks on English and Swedish brandy-drinking, gravely asks the question, whether the red noses of the English dram-drinkers are not due to the various adulterations introduced into the liquors by British dealers?

Boston M. & S. J., *Oct. 4, 1854*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

HUNTER—Francis T. Hunter, M.D., of Chestnut Hill, died on September 7. He was in his fifty-eighth year.

Dr. Hunter received his degree from Harvard Medical School in 1924. He was director of the laboratory, Baker Memorial Hospital, Massachusetts General Hospital, a member of the staff of Massachusetts Eye and Ear Infirmary, a fellow of the American Medical Association and formerly a trustee of the Boston Medical Library.

He is survived by his widow, a daughter and a son.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

ORTHOPEDIC CLINIC	DATE	CLINIC CONSULTANT
Salem	October 4	Paul W. Hugenberger, M.D.
Gardner	October 5	Carter R. Rowe, M.D.
Greenfield	October 7	Charles L. Sturdevant, M.D.
Lowell	October 8	Albert H. Brewster, M.D.
Lynn*	October 11	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Haverhill	October 13	William T. Green, M.D.
Brockton	October 14	George W. Van Gorder, M.D.
Worcester	October 15	John W. O'Meara, M.D.
Springfield	October 19	James D. Fisher, M.D.
Pittsfield	October 20	Edward J. Coughlin, Jr., M.D.
Fall River	October 25	David S. Grice, M.D.
Hyannis	October 28	Paul L. Norton, M.D.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

RHEUMATIC-FEVER CLINIC	DATE
Fitchburg	October 6, 13, 20, 27
North Reading	October 5, 19, 26

PLASTIC CLINIC	HELD	CONSULTANT
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Hypertension and Nephritis. By Arthur M. Fishberg, M.D., director of medicine, Beth Israel Hospital, New York City, and clinical professor of medicine, Post-Graduate Medical School of New York University. Fifth edition. 8°, cloth, 986 pp., with 49 illustrations. Philadelphia: Lea and Febiger, 1954. $12.50.

The last revision of this standard special book was made over fifteen years ago, and this new edition has been rewritten and thoroughly revised. Seven chapters have been added on the individual processes in urine formation, diabetic glomerulosclerosis, chronic pyelonephritis, dietetic, pharmacologic and surgical treatment in essential hypertension, and hypertension in pheochromocytoma and Cushing's syndrome. Extensive bibliographies are appended to the 27 chapters, and there is a good index. The book should be in all medical libraries and available to all physicians.

Acute Renal Failure. By Arthur Grollman, Ph.D., M.D., F.A.C.P., professor of experimental medicine, Department of Experimental Medicine, and lecturer in pharmacology and toxicology, Southwestern Medical School of the University of Texas, attending physician, Parkland Hospital, consultant in internal medicine, Baylor University Hospital, and consultant in biochemistry and physiology, Veterans Administration Hospital, Dallas, Texas. 8°, cloth, 96 pp., with 6 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $4.00. (Publication No. 192, *American Lecture Series.*)

Dr. Grollman has correlated and evaluated the pertinent literature on acute renal failure, with special emphasis on pathogenesis and treatment. The condition is discussed under the headings of etiology, pathology, physiology, clinical course and treatment. There is a bibliography of 103 references and a good index. This is a practical and valuable monograph.

Third Annual Report on Stress. By Hans Selye, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada), professor of medicine and director of the Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal; and Alexander Horava, M.D. (Lausanne), research associate and librarian of the Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal. 8°, cloth, 637 pp., with illustrations. Montreal: Acta, Incorporated, 1953. $10.00.

This volume is the third of a series of annual supplements to *Stress: The physiology and pathology of exposure to stress,* published in 1950. The volumes are designed as guides to the entire literature on the subject. The text is divided into 3 parts on the general and special physiology and pathology of stress, and a sketch for a unified theory of medicine. There is an atlas of 6 plates, a bibliography of 188 pages and a comprehensive index. The publishing is excellent.

Problems of Consciousness: Transactions of the fourth conference, March 29, 30 and 31, 1953, Princeton, N. J. Edited by Harold A. Abramson, M.D., assistant clinical professor of physiology, Columbia University College of Physicians and Surgeons, and associate attending physician for allergy, Mount Sinai Hospital, New York City. 8°, cloth, 177 pp., with illustrations. New York: Josiah Macy, Jr., Foundation, 1954. $3.25.

At this conference the following topics were discussed: problems of consciousness—a review, an analysis and a proposition; consciousness and symbolic processes; and the problem of consciousness in child psychology — developmental changes in awareness.

Surgical Infections: Prophylaxis, treatment, antibiotic therapy. By Edwin J. Pulaski, M.D., D.M.Sc. (Surgery), Lieutenant Colonel, Medical Corps, United States Army, deputy director, Division of Surgery, Walter Reed Army Medical Center, and assistant chief, Surgical Service, Walter Reed Army Hospital. 8°, cloth, 332 pp., with 5 tables and 10 charts. Springfield, Illinois: Charles C Thomas, 1954. $7.75. (Publication No. 170, *American Lecture Series.*)

This monograph stresses the importance of surgical principles and practices, putting the antibiotics in their proper place as valuable adjuncts, and warns against the indiscriminate use of these agents. The text is divided into 2 parts: antibiotic therapy and the management of surgical infections. Lists of references are appended to the chapters. The text concludes with 3 tables on the distribution of penicillin, streptomycin and chlortetracycline in body fluids (estimated in hours after a single dose). There are lists of references for the tables and for the text in general, as well as a good index.

Lung Cancer. By Seymour M. Farber, M.D., associate clinical professor of medicine, University of California Medical School, and lecturer in diseases of the chest, University of California School of Public Health. 8°, cloth, 157 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $4.75. (Publication No. 187, *American Lecture Series.*)

The author discusses the etiology, histopathology, clinical features, roentgenology, diagnostic studies, surgery and nonsurgical treatment of cancer of the lung. There is a bibliography of 134 references and a good index.

A Formulary for External Therapy of the Skin. By Chester N. Frazier, M.D., Dr.P.H., Edward Wigglesworth Professor of Dermatology, Harvard Medical School, and chief of the Dermatological Service, Massachusetts General Hospital; and Irvin H. Blank, Ph.D., research associate in dermatology, Harvard Medical School and Massachusetts General Hospital. 8°, cloth, 118 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $3.25. (Publication No. 201, *American Lecture Series.*)

This formulary was originally compiled for the general use of the clinical staff of the Massachusetts General Hospital. The beginning chapters, which consider the evolution of the formulary, objectives of external therapy and some principles of treatment, are followed by chapters on cleansing the skin, ointment vehicles, emollients and protectives, antipruritics, anti-infectives, antieczematous and antiseborrheic agents and antiperspirants. Lists of references are appended to the chapters, and there is a good index.

Menorrhalgia — Menstrual Distress. By William Bickers, M.D., diplomate, American Board of Obstetrics and Gynecology, and attending gynecologist to the Retreat for Sick and the Sheltering Arms, Richmond Community and Evangeline Booth hospitals, Richmond, Virginia. 8°, cloth, 97 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $2.75. (Publication No. 208, *American Lecture Series.*)

The author discusses the physiology and morphology, etiology, hormonal interceptors and excitors, pharmacophysiodynamics, surgery, clinical evaluation and general treatment of menorrhalgia, including dysmenorrhea, premenstrual tension and pelvic vascular congestion. Lists of references are appended to the chapters, and there is a good index.

French's Index of Differential Diagnosis. Edited by Arthur H. Douthwaite, M.D., F.R.C.P., senior physician, Guy's Hospital, and honorary physician, All Saints' Hospital for Genito-urinary Diseases. Seventh edition. 4°, cloth, 1046 pp., with 731 illustrations of which 200 are in color. Baltimore: Williams and Wilkins, 1954. $20.00.

This standard reference volume, first published in 1912, has gone through 7 editions and a number of reprintings to date. In the seventh edition the book has been completely revised and is now the joint work of 18 contributors and the editor. The material is arranged alphabetically by subjects; there is a comprehensive index of 146 pages, and the publishing is good. The book should be in all medical libraries and should be of value to the physician for quick reference.

Nurse and Patient: An ethical consideration of human relations. By Evelyn C. Pearce, S.R.N., R.F.N., S.C.M., M.C.S.P., formerly, senior nursing tutor, Middlesex Hospital, London, and member of the General Nursing Council for England and Wales (1937-51). Foreword by the Rt. Hon. the Lord Webb-Johnson, G.C.V.C., C.B.E., D.S.O., T.D., F.R.C.S., LL.D., honorary fellow, American College of Surgeons, consulting surgeon to the Middlesex Hospital, past president of the Royal College of Surgeons of England and of the Royal Society of Medicine. 8°, cloth, 182 pp. Philadelphia: J. B. Lippincott Company, 1954. $3.00.

In this unusual book Miss Pearce discusses the relation of the nurse to the patient and the position of the nurse in the health team. The text is divided into 3 parts: the patient, the nurse and patients and nurses as people. A list of references and an index conclude the text. The small book should be in all collections on nursing.

Transactions of the New England Obstetrical and Gynecological Society. Edited by Robert M. Green, M.D., Boston. Vol. 7 (1953). 8°, paper, 217 pp., with illustrations. Published by the Society, 1954. Free.

The papers read at the spring and annual meetings of the society are included in this volume. The annual meeting featured two panel discussions — one on pruritus vulvae and pruritus ani and one on endocrine glands in obstetrics. From small beginnings the society has grown to one of importance, with a membership of nearly 700.

Energy Metabolism and Nutrition. By Professor Raymond W. Swift and Cyrus E. French, Department of Animal Nutrition, Pennsylvania State University. 8°, cloth, 264 pp., with illustrations. Washington, D.C.: Scarecrow Press, 1954. $5.75.

In this monograph the authors bring together the various direct and indirect methods of colorimetry and point out the applicability and limitations of each in modern nutrition. The pertinent literature is surveyed, and the material is primarily presented for seniors and postgraduate students. The text is divided into three parts: underlying principles, methods and experimentation. The references are given as footnotes to the pages. The text is concluded with tables of reference data. There are indexes of authors and subjects. The book should prove useful as a reference source.

An Atlas of Congenital Anomalies of the Heart and Great Vessels. By Jesse E. Edwards, Thomas J. Dry, Robert L. Parker, Howard B. Burchell, Earl H. Wood and Arthur H. Bulbulian of the Mayo Clinic and Mayo Foundation. Second edition. 4°, cloth, 216 pp., with 491 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $13.50.

This new edition of an atlas first issued in 1948 has been revised and greatly expanded. It is the composite work of 6 physicians and scientists of the Mayo Clinic and Mayo Foundation. Twelve additional malformations are included, and each of the sections has been expanded in greater detail. A number of conditions are also described on which data were obtained by the study of patients in the physiologic laboratory by such technics as cardiac catheterization, oximetry, dye dilution and intra-arterial-pressure studies. There is a bibliography of 25 quarto pages arranged by topics and comprising all the important articles on the subject. There is a good index, and the publishing is excellent. The atlas should be in all collections on cardiology.

A Curriculum for Schools of Medical Technology. Editor, Israel Davidsohn, M.D., professor of pathology and chairman, Department of Pathology, Chicago Medical School, director of laboratories and pathologist, Mount Sinai Hospital, and director of research, Mount Sinai Medical Research Foundation, Chicago, Illinois; associate editor, Kurt Stern, M.D., director, Blood Center of Mount Sinai Medical Research Foundation and Hospital, and assistant professor of pathology, Chicago Medical School. Third edition, recommended by the Board of Registry of the American Society of Clinical Pathologists. 4°, paper, 122 pp., with illustrations. Muncie, Indiana: Registry of Medical Technologists, 1953. $3.00.

The first edition of this curriculum was published in 1937. The text of this new edition has been completely rewritten and brought up to date and up to the required standards of the registration board. Seven persons—6 physicians and a general scientist — have collaborated in writing the text. References are appended to each subject, and there is a long bibliography consisting of 9 textbooks for required reading assignments, a list for collateral reading and lists of dictionaries and periodicals. There is a good index.

Atlas of Exfoliative Cytology. By George N. Papanicolaou, M.D., Ph.D., clinical professor of anatomy emeritus, Cornell University Medical College. 4°, cloth, 234 pp., with 36 plates. Cambridge, Massachusetts: Harvard University Press, 1954. (Published for The Commonwealth Fund.) $18.00.

This atlas is made up of 36 plates, 24 of which are in color by the noted artist Hashime Murayama, a specialist in this type of work. They are exceptionally well done. The cell forms used for illustration have been limited to those "whose derivation may be considered fairly well established and which appear to be representative of distinct cell types." There are 56 pages of preliminary text, including a brief historical survey. There is a short bibliography and a good index, and the publishing is excellent. The atlas should be in all collections on cytology.

NOTICES

PARAPLEGIA CONFERENCE

The third annual paraplegia conference of the Department of Medicine and Surgery of the Veterans Administration will be held at the West Roxbury Veterans Administration Hospital, West Roxbury, Massachusetts, October 12-14. Dr. Herbert S. Talbot, chief of the Paraplegia Service, will be chairman.

Physicians are invited to an open session to be held in the recreation hall of the hospital on October 13, at 8:30 p.m. The program is as follows:

A Dynamic Splint for Paralyzed Hands. Drs. Henry Marble and John G. Bisgrove.

Surgical Principles in the Treatment of Pressure Ulcers. Dr. Bradford Cannon.

The Treatment of Cord Injuries outside Veterans Administration Hospitals. Dr. Donald Munro.

AMERICAN TRUDEAU SOCIETY

An interim scientific session of the American Trudeau Society will be held at the Hotel New Yorker, New York City, November 17, from 9 a.m. to 5 p.m. The meeting will be open to physicians and scientists interested in pulmonary diseases from the clinical and laboratory standpoints.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER, 1954–APRIL, 1955. Postgraduate Medical Institute. Page 451, issue of September 9.

SEPTEMBER 30–OCTOBER 2. Canadian Society for the Study of Fertility. Page 285, issue of August 12.

OCTOBER 1 and DECEMBER 3, 1954; FEBRUARY 4 and APRIL 1, 1955. New England Society of Anesthesiologists. Page 1054, issue of June 17.

OCTOBER 4–28. Consultation Clinics for Crippled Children in Massachusetts. Page 586.

OCTOBER 4–DECEMBER 8. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

OCTOBER 4, 1954–JANUARY 17, 1955. Hartford Medical Society. Page 496, issue of September 16.

OCTOBER 6. Massachusetts Medical Society. Stated Meeting of the Council. Page 493, issue of September 16.

OCTOBER 7 and 8. Pan-Pacific Surgical Association. Page 1092, issue of June 24.

OCTOBER 8. New England Society of Anesthesiologists. Page 544, issue of September 23.

OCTOBER 8 and 9. Academy of Psychosomatic Medicine. Page 748, issue of April 29.

OCTOBER 11–15. American College of Physicians Course. Page 44, issue of July 1.

OCTOBER 12–14. Paraplegia Conference. Notice above.

OCTOBER 14. New York Diabetes Association. Page 544, issue of September 23.

OCTOBER 16–22. American Occupational Therapy Association. Page 1092, issue of June 24.

OCTOBER 18–29. New York Academy of Medicine Graduate Fortnight. Page 44, issue of July 1.

OCTOBER 22. National Vitamin Foundation Symposium. Page 410, issue of September 2.

OCTOBER 22 and 23. American Trudeau Society (Eastern Section). Page 544, issue of September 23.

OCTOBER 25–27. New England Postgraduate Assembly. Hotel Statler, Boston.

OCTOBER 25–27. National Gastroenterological Association. Page 496, issue of September 16.

OCTOBER 25–30. Course in Care of Atomic Casualties. Page 285, issue of August 12.

OCTOBER 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

OCTOBER 27–29. International Symposium on the Hypophyseal Growth Hormone. Page 1092, issue of June 24.

OCTOBER 29. Massachusetts Public Health Association. Fall Meeting. Blake's Restaurant, Springfield, Massachusetts.

OCTOBER 31–NOVEMBER 4. American Institute of Dental Medicine. Page 968, issue of June 3.

NOVEMBER, 1954–MAY, 1955. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

NOVEMBER 2–5. Fourth Annual Bay State Rehabilitation Conference. Hotel Statler, Boston.

NOVEMBER 3 and 4. M & R Pediatric Research Conference. Page 496, issue of September 16.

NOVEMBER 3–5. National Society for Crippled Children and Adults. Page 44, issue of July 1.

NOVEMBER 6. Massachusetts Hospital School Symposium. Page 495, issue of September 16.

NOVEMBER 12. Memorial Center for Cancer and Allied Diseases Conference. Page 544, issue of September 23.

NOVEMBER 12 and 13. Inter-Society Cytology Council. Page 968, issue of June 3.

NOVEMBER 15–19. American College of Surgeons. Page 496, issue of September 16.

NOVEMBER 15–26. Laboratory Diagnosis of Tuberculosis Course. Page 246, issue of August 5.

NOVEMBER 17. American Trudeau Society. Notice above.

DECEMBER 5. American Academy of Dental Medicine. Page 1092, issue of June 24.

DECEMBER 8. New England Pediatric Society. Page 968, issue of June 3.

DECEMBER 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.

JANUARY 3–MAY 9, 1955. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

JANUARY 10–15. Course in Care of Atomic Casualties. Page 285, issue of August 12.

FEBRUARY 7–9. McIntyre-Saranac Conference. Page 410, issue of September 2.

FEBRUARY 11–25. Pan-American Academy of General Practice. Page 496, issue of September 16.

MARCH 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.

MAY 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.

JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, OCTOBER 7

THURSDAY, OCTOBER 7

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*10:00–11:00 a.m. Surgical Rounds. 5th floor teaching unit, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*11:00 a.m. Thoracic Conference. The Embryological Development of the Heart and the Origin of Certain Congenital Anomalies. Main Amphitheater, Peter Bent Brigham Hospital.

(Notices concluded on page xv)

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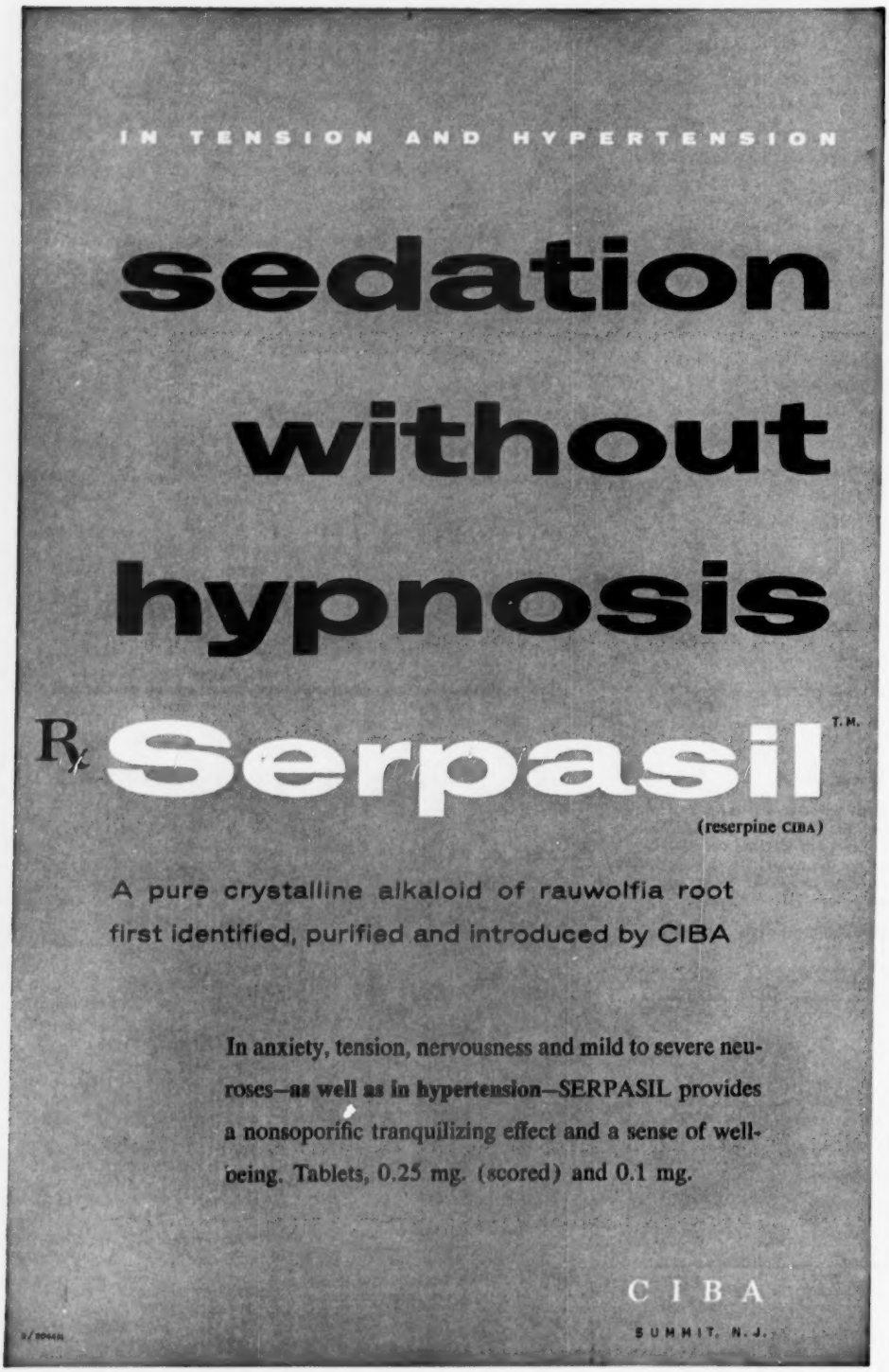
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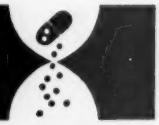

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—ROGERS, H.L.: Ann. Allergy 12:266 (May-June) 1954.

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—GREEN, M.A.: Ann. Allergy 12:273 (May-June) 1954.

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—MULLIGAN, R.M.: J. Allergy 25:358 (July) 1954.

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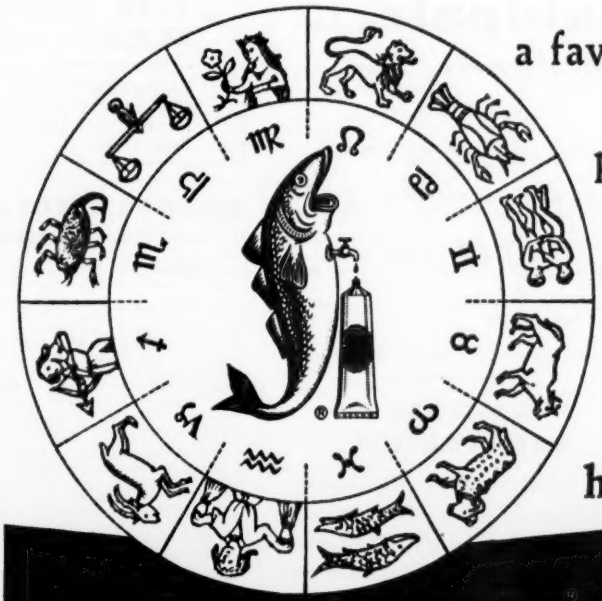

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1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. M. 53:2233, 1953.
2. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951.
3. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgery 18:512, 1949.
4. Turell, R.: New York St. J. M. 50:2282, 1950.

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NOTICES *(Concluded from page 588)*

*12:00 m.–1:00 p.m. Adventures in Cardiology. Dr. Paul White. Stearns Auditorium, New England Center Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital (Burnham 4), Massachusetts General Hospital.

FRIDAY, OCTOBER 8

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30 a.m. New England Society of Anesthesiologists. Mary Hitchcock Memorial Hospital, Hanover, New Hampshire.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital (Burnham 4), Massachusetts General Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, OCTOBER 9

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*10:30 a.m.–12:00 m. Surgical History Meeting. Stearns Auditorium, New England Center Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, OCTOBER 11

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Therapeutic Conference. Dr. McCombs, moderator. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–8:00 p.m. Pathology Conference. Dr. MacMahon and Staff. Stearns Auditorium, New England Center Hospital.

TUESDAY, OCTOBER 12
Holiday

WEDNESDAY, OCTOBER 13

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th floor teaching unit, Beth Israel Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. Out-Patient Department.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.
*8:30 p.m. Paraplegia Conference. Recreation Hall, West Roxbury Veterans Administration Hospital.

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